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In Exclusive Interview:

Dr. Cooper Defends Swine-Type Flu Shots

'We Had No Choice . . . but to Take the Action We Did,' Says HEW Official

Medical Tribune Report

WASHINGTON—In an exclusive interview amid rising debate on the crash program to immunize over 200 million Americans against swine-type influenza, Dr. Theodore Cooper, Assistant Secretary for Health, Department of Health, Education and Welfare, stressed that the government's vaccination decision was an essential and responsible one based on fundamental scientific judgments in the absence of hard data.

"We had no choice as public officials but to take the action we did to protect the public health, even though we do not know for sure there will actually be an epidemic of influenza this fall or winter," Dr. Cooper said.

Besides the validity of mounting such a program, areas covered in the interview by Dr. Arthur M. Sackler, International Publisher of MEDICAL TRIBUNE, included: Why the vaccine was not stockpiled and other options utilized, why the government does not embark on crash programs for other "epidemic" diseases such as cardiovascular disease, and the differences in handling the vaccine program and

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DR. COOPER

Dr. Sackler Questions Gov't Procedures: Text of Interview: Part I

It seems to me that the decision for our national effort to head off a swine flu epidemic is based not on hard data but rather on scientific judgment. Is that true?

You are right as rain about the decisions involved in this program. They are based on medical and scientific judgments. Frequently I am asked if the swine flu program sets a precedent for similar actions against other influenza viruses or other diseases in the future. I reply that these will have to be judged on their own merits just as this issue was decided by the best public health and scientific expertise we could bring to bear.

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Immunologic Link?

Progesterone Seen Preventing Fetal Rejection

By NATHAN HORWITZ
Medical Tribune Staff

SAN FRANCISCO—Evidence that progesterone may be a vital link in preventing immunologic rejection of the fetus by the mother was reported here by a team at the University of California San Francisco.

Studies showing that the hormone exerts a powerful local immunosuppressive effect within the placenta, thereby protecting the fetus against rejection, were described by Pentti K. Siiteri, Ph.D., who said the findings could have far-ranging implications in transplantation surgery and in the treatment of spontaneous abortion.

Speaking at the meeting of the Endocrine Society, Dr. Siiteri, who is Professor of Obstetrics-Gynecology at UCSF, said the team's animal experiments and in vitro studies of human cell cultures have provided the first evidence for the long-held but never confirmed hypothesis that progesterone may exert the same immunosuppressive in utero effect as that of cortisol or glucocorticoids in transplantation management.

An important observation to emerge from the studies, Dr. Siiteri reported, is

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Tumor-Specific Antigen Aids Recovery from Lung Cancer

By KRISTIN WHITE
Special Tribune Correspondent

NEW YORK — Mobilizing the immune system to eliminate any lung cancer cells lingering after surgery and adjuvant chemotherapy offers dramatic therapeutic promise, according to Drs. Thomas H. M. Stewart and Jules E. Harris, of the University of Ottawa, and Ariel C. Hollinshead, Ph.D., Professor of Medicine at George Washington University Medical Center in Washington, D.C.

Dr. Hollinshead was recently elected Medical Woman of the Year "in recognition of her pioneer work in separating tumor-related antigens from the cell surface, and in showing the reactivity of purified antigens for specific types

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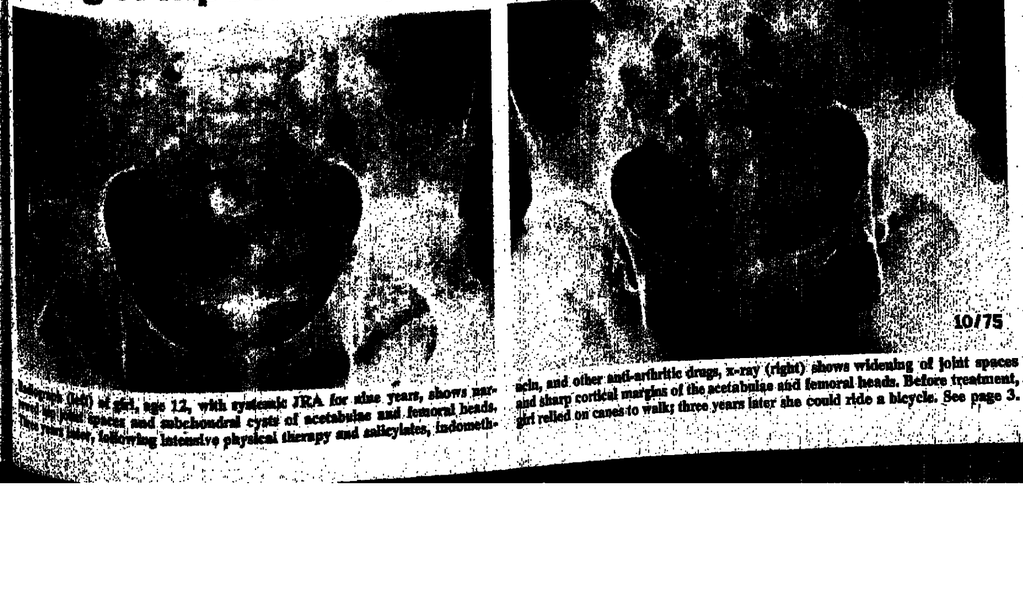
Healing of Hip Joint May Avoid Surgery in Juvenile Arthritis



Radiographs (left) of girl, age 12, with systemic JRA for nine years, shows narrowed hip joint spaces and subchondral cysts of acetabulae and femoral heads. Three years later, following intensive physical therapy and salicylates, indomethacin, and other anti-arthritic drugs, x-ray (right) shows widening of joint spaces and sharp cortical margins of the acetabulae and femoral heads. Before treatment, girl relied on canes to walk; three years later she could ride a bicycle. **See page 3.**

INTERNATIONAL REPORT

from Britain *from the Editors of Medical News-Tribune, London*

Expert Suggests Looking for Scurvy in 'Gout' Patients

Medical Tribune World Service

LONDON—At a recent meeting organised by the Wellcome Medical Division, Professor W. W. Buchanan, of the University of Glasgow, discussed the differential diagnosis of gout and reminded the audience that it was more serious to miss an acute cellulitis or an acute suppurative arthritis than to miss a diagnosis of gout.

Also, he said, in April or May acute scurvy should be thought of. In Glasgow, 40 such cases present about that time, usually with an acute arthritis followed the next day by what may look like flea bites. These are perifollicular haemorrhages, and the joint should be checked for intra-articular haemorrhage.

It was also worth remembering, Professor Buchanan said, that not all joint pain in a gouty patient need be due to gout. Injury may be a cause.

He described the patient whose gout had been well controlled for two years but who began to have neck pains.

This turned out to be due to fractures of the cervical vertebrae in a whiplash injury two months previously.

Dr. J. T. Scott, Consultant Physician at the Charing Cross Hospital and the West London Hospital, London, advised against subjecting all patients with acute gout to continuous treatment to reduce serum uric acid levels, unless the following indications were present: tophi and joint damage, frequent acute attacks, impaired renal function or a serum uric acid beyond 8 mg per 100 ml.

He added that, although an impaired renal function is generally accepted as one of the indications for maintenance

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Author and gout sufferer Richard Gordon, seated, demonstrates a "gout stool" to Dr. J. T. Scott, of Charing Cross Hospital. At the London meeting on gout, Mr. Gordon said his condition was first diagnosed as a sesamoid bone fracture.

from France *from the Editors of Tribune Medicale, Paris*

French 'Liver Attack' Nonexistent, Hepatologists Say

Medical Tribune World Service

PARIS—There is no such thing as a "liver attack," members of the French Society for the Study of the Liver were told at the society's first conference, held under the direction of Prof. Jean-Pierre Benhamou, of Hopital Beaujon, Clichy. Hepatologists have never encountered it, he said.

This typical French "ailment" is only a myth, unconsciously supported by both physicians and patients, according to Prof. D. Dhumeaux, of Hopital Henri Mondor, Creteil, who is vigorously combating it. The consequences of this popular belief in liver "trouble" are not as harmless as they may seem initially, primarily because the real causes of various malfunctions are not uncovered.

According to reports at the conference, in most cases the "liver attack"—or "crisis," as the French call it—begins in the morning with a headache, a coated tongue, nauseau and vomiting, which may contain bile. Because the liver secretes bile, it is blamed. But the normal stomach may contain bile.

The "liver crisis" is often accompanied by right subcostal pains, the origin of which is probably not hepatic.

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from Germany *from the Editors of Medical Tribune Germany, Wiesbaden*

Ultrasound Observation Reduces Risks in Amniocentesis

Medical Tribune World Service

DUSSELDORF—A newly developed ultrasonic technique has definitely reduced the risks of amniocentesis by providing data beforehand on the position of the fetus and placenta, and by allowing constant observation of fetus and needle during the procedure, Dr. A. Terinde, of Dusseldorf University Women's Clinic, reported here at the clinic's Seventh Medical Diagnosis Week.

The most favorable time for amniocentesis is in the 15th or 16th week of pregnancy, Dr. Terinde said. Even so, spontaneous abortions may still occur. Difficulties are mainly due to placentae lying contiguous to the anterior wall of the uterus, which happened in 30% of 52 women examined. The technique is also impeded by myomata.

When monitoring the amniocentesis procedure, the ultrasonic head is placed on the mother's abdomen. Under given circumstances; the video-type image allows the direction of the perforation to be altered.

The great advantage of ultrasound control is evidenced by the presence of bloodstained amniotic fluid in only three amniocenteses in a recent series.

In more than 50% of the cases, pains began after the amniotic perforation. It is therefore advisable to administer a pain inhibitor after each procedure, Dr. Terinde said. Rhesus-negative women should be given 30 micrograms anti-D-immunoglobulin, even when it is certain that the placenta has not been damaged.

from Japan *from the Editors of Medical Tribune Japan, Tokyo*

Protection Urged for X-Ray, Isotope Workers' Fingertips

Medical Tribune World Service

OKAYAMA—Taken together, the results of several studies strongly suggest that medical, paramedical, and dental personnel who work with x-rays or radioactive isotopes should take particular precautions to prevent radiation exposure to the hands and fingertips, Professor Yukio Koga, of the Department of Radiology, Nagoya Eisei College, told the 49th meeting of the Japanese Society of Occupational Health.

Separate surveys conducted by Dr. Koga have revealed the following:

- A study initiated in 1970 among isotope researchers disclosed that the hand was the most frequently exposed part of the body. Several subjects participating in that study complained of abrasion of the fingertips.
- Since 1970, 83 deaths among medical personnel have been reported due to radiation exposure in the working environment. These include 36 deaths from skin cancer, 29 from leukemia, nine from aplastic anemia, and nine others, most of which were due to skin ulcers on the hand.
- Among the 222 members of the Society of Nuclear Medicine who responded to a questionnaire designed to estimate a week's consumption of the popularly used isotope 99MTC, 70% admitted to handling the isotope with bare hands. Analysis of the responses also showed that 20% handled the isotope at the rate of 100 mCi per week

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Risk of radiation exposure to the fingertips is suggested by finding that 3.9% of 102 physician-members of the Japanese Society of Medicoradiation have abnormal fingerprints, right. Normal print, left, has fewer wrinkles and deeper furrows. Since 1970, 83 deaths among medical personnel have been reported due to radiation exposure in the working environment.

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'Genetic Engineering' Storm Brews Anew

By ANASTASIA TOUFEXIS
Medical Tribune Staff

CAMBRIDGE, MASS.—The storm brewing over "genetic engineering" or recombinant DNA research recently erupted anew in this university town. Within the short span of one month, during this past June, two local events, and another more national in scope, converged to almost set this community on its intellectual ear.

First, a scientific symposium at the Massachusetts Institute of Technology (MIT) raised the issue of the potential impact on society of recombinant DNA research.

Next, the City Council of Cambridge began holding public hearings on whether Harvard University should be granted permission to build a high-security laboratory where such research could be carried out.

Then, at the end of the month, the National Institutes of Health (NIH) issued formal guidelines for federally-funded recombinant research, setting safety standards and restricting the areas investigators might pursue.

The concern centers around a revolutionary new area of molecular biology, also referred to as "gene transplantation" or "genetic grafting." Within the last few years, scientists have devised a technology which makes it theoretically possible to cross evolutionary genetic barriers to create "unnatural" organisms.

Mixing Toads and E. Coli

New techniques enable researchers to splice fragments of DNA from one species, for example a toad, into a piece of DNA, called a vehicle or vector, from another species, say a bacterium, and then to implant the "recombined" DNA molecule into the bacterium host, most commonly Escherichia coli K-12. The foreign DNA is thus incorporated into the host where it replicates, multiples, and hopefully expresses itself.

The potential benefits are enormous. Although scientists caution they are "blue-skying," they foresee practical applications in industry, agriculture and medicine. For example, implanting specific genes into various hosts may yield microbes which can "eat" oil spills, plant organisms which fix nitrogen from the air and thus require no fertilizer, bacteria which can act as antibiotic factories, mammalian cells which can synthesize specific proteins or hormones, such as insulin, or correct genetic disorders, including sickle cell anemia and phenylketonuria.

On the other hand, some experiments might confer new properties to host microbes, for example resistance to a specific drug, or produce novel organisms which could wreak havoc on the environment and the populace, were they to escape from the laboratory.

It is the latter possibilities which disturb the public. The extent of this concern can perhaps be gauged by the Cambridge City Council hearings on Harvard University's intention to build a laboratory for recombinant research.

Over 400 people jammed the chamber and galleries in 100° heat, spilling out to the hallways, to hear speakers from Harvard, from MIT, from NIH and from the local community debate the dangers and merits of DNA research. The five-and-a-half hour first meeting adjorned with the city council ordering a three-month moratorium on recombinant DNA research.

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N.J. Cardiologists Defy FDA, UGDP on Hypoglycemic Drugs

Medical Tribune Report

TRENTON, N.J.—Nearly seven years after the University Group Diabetes Program issued its first report, how much credibility do its controversial findings enjoy among practicing physicians?

To find out what one major specialty thinks, a New Jersey Health Department official polled the state's cardiologists—and has come up with some surprising results.

Dr. Arthur Krosnick, Coordinator of the Health Department's Diabetes Control Program, reports that over half of New Jersey's members of the American College of Cardiology responded to his questionnaire, and that "most responding cardiologists" do not accept the UGDP conclusions about oral hypoglycemic drugs.

'Salty' Comments

The UGDP's central finding—and the core of the subsequent controversy—was that "an excess of cardiovascular deaths" occurred among patients on the oral agents. Critics in the U.S. and abroad have asserted that these findings were open to serious quetion because of the study's methodology, patient selection, methods of treatment and satistical procedure.

"Of the heart specialists who answered the questionnaire, 80% prescribe the oral hypoglycemic drugs for *both* their cardiac patients with diabetes and the non-cardiacs in their practice," Dr. Krosnick declared. "Seventeen percent of the physicians do not prescribe the drugs for cardiacs, while 12% withhold the drugs for non-cardiac diabetics."

He added that written comments on the UGDP study by a "number of cardiologists" were "too salty to print."

The Food and Drug Administration also came under attack for its action in proposing relabeling of the oral antidiabetic drugs, Dr. Krosnick disclosed. The agency's proposal provoked "a degree of resentment" among respondents and was characterized as revealing "an overbearing attitude," he said.

One cardiologist called on the FDA to "settle uncertainties about drugs *before* they are approved for distribution" and urged that "scientific questions be settled in a scientific manner and not debated before press conferences."

Dr. Krosnick's report on the poll was printed in the June issue of the *Journal of the Medical Society of New Jersey*.

The health official said that he decided to poll cardiologists because the cardiovascular implications of the UGDP findings impinge directly on this specialty's area of expertise. The survey sought to find out to what extent cardiologists were familiar with the UGDP study, whether they were informed about the issues and the course of the controversy surrounding the study; and, most important, what impact the widely-publicized, prolonged debate has had on their use of oral hypoglycemics in diabetics with and without heart disease.

A total of 225 questionnaires were mailed to all of the New Jersey members of the American College of Cardiology, and 139 (62%) were returned, including 20 (54%) which were completed, Dr. Krosnick stated.

Of the respondents, 94% had heard of the UGDP study, 88% were familiar with the results and recommendations. Eighty-two percent were aware of the FDA's position and its proposed relabeling changes.

"It appears that the majority of New Jersey cardiologists who responded are familiar with the UGDP and FDA reports," Dr. Krosnick commented. "Despite this knowledge, most of them continue to use the oral hypoglycemic drugs in both cardiac and non-cardiac diabetic patients and do not require informed consent. Of the small number who do not prescribe the oral hypoglycemics, about half stopped recommending them because of the UGDP-FDA reports."

Healing of Hip Joint May Avoid Surgery In Juvenile Arthritis

By NATHAN HORWITZ
Medical Tribune Staff

CHICAGO—Presumptive evidence that hip joint restoration may occur in youngsters with juvenile rheumatoid arthritis has been reported by a California team.

In what may be the first documented demonstration that joint destruction in JRA is reversible in some instances at least, the group presented radiographic evidence suggestive of hip joint healing in six children.

The X-ray data showed widening of hip joint spaces, filling in of erosions, reduction or resolution of subchrondral cystic changes, and "impressive remodeling of the femoral and acetabular surfaces," according to Dr. Bram Bernstein, Associate Clinical Professor of Pediatrics, University of Southern California.

The findings, which have implications for rehabilitative programs in JRA, were described by Dr. Bernstein at the annual meeting of the American Arthritis Foundation.

In the series of six children, four girls and two boys, the onset of JRA was systemic in five and polyarticular in one. Ages of onset ranged from 2½ to six years. Each of the patients showed "a dramatic decrease" in disease activity and improvement in hip motion between ages 11 to 16, Dr. Bernstein reported. Radiographic stud-

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Current Opinion

Double-Blind and Clinical Observation

by CHARLES HARRIS, M.D., F.A.C.P.
Toms River, N.J.

THE TERM, DOUBLE BLIND, has become to scientific jargon what "In God We Trust" once meant to numismatists. What has happened to our coinage is obvious and similarly some vaunted double blind studies may also turn out to be amalgams of fact and fancy.

Statistics is a delicate mathematical technique devised to estimate the truth of a universal sample. If indeed 70% of Americans had brown eyes, this fact could be estimated by determining eye color of smaller samples. If in choosing samples, one hundred individuals were counted in which 70% had blue eyes, statistical computation will tell you what the odds are of choosing 70 blue eyed individuals from a population in which 70% had brown eyes. By convention, if the odds of making this choice were less than 5% when choosing by chance alone, then the probability exists that some blond blue eyed foreigners were smuggled into the sample, or the sample represented a long-shot choice.

The Null Hypothesis

The null hypothesis states that there is no difference between the groups of data being examined. If the data are so disparate between groups that the odds of their being chosen from the same group is 5% or less, then statisticians might consider that the null hypothesis has been rejected, and that the two groups represent different populations. On the other hand, if the groups differ, but there is a 10% possibility that the difference could be accounted for by chance alone, then the null hypothesis is accepted, and the groups of data represent the same population.

This is an imposing tool without which much research would crawl at a snail's pace. As a matter of fact, without calculators and computers, statistics would crawl at a snail's pace, because the computations are becoming too cumbersome to perform by hand in a reasonable period of time.

From Single to Double Blind

The concept of double blind became popular with studies of drug efficacy. The medication to be tested was usually assigned to a physician at a center from which a more or less uniform population would be drawn—a nursing home, a prison, a university, the armed services. If, for instance, a sleeping tablet were being tested, half the group would get the sleeping tablet, the other half would receive a placebo. Care was taken to dress the sleeping tablet and placebo in the same jackets so that the subject would be fooled. This was the single blind study. A scoring system was then set up to determine the quality of sleep enjoyed by each group and the scores compared statistically.

It soon became apparent that if the doctors knew which patient received the real and which the spurious drug, as scorekeepers they might be biased in designating the scores. As a result, the double-blind study was born in which not only the patients, but the doctors were kept in ignorance of which capsule contained the real thing. The technique of the double-blind study is ingenious and useful, but those qualities do not require that double-blind studies be blindly accepted.

What Statistics Do

Statistics are useful in making educated guesses about the meaning of contemporary events and useful in formulating projections. They hover about the truth like a boat on a mooring, without ever actually touching it.

About Dr. Harris:

Dr. Charles Harris, whose training earned certification in pathology and eligibility in medicine, has spent two decades in cancer research: the first at a university research institute; the second at a geriatric institution where he bartered service to the department of medicine for the use of their research laboratories.

Prior to going into private practice, he served briefly as medical director for a community health center. His book, One Man's Medicine (Harper & Row, 1975), is a literary paraphrase of these experiences.

In his book, Dr. Harris concludes that it is in private practice that the physician can best serve his patient. After experience on both sides of the institutional fence, Dr. Harris feels that the physician must marshal the facilities of the medical apparatus on behalf of his patients, rather than be an agent of institutions in the care of patients. He cites two reasons to support this view: first, responsibility and authority cannot be divided; secondly, neither institutions nor governments are licensed to practice medicine: physicians are—Editor.

Another estimate of the truth, of course, is experience. If, for example, the majority of the population zeros in on a certain sleeping potion and "swears by it," the odds are that the medication is probably effective and for the near term relatively harmless. If something as dramatic as penicillin appears on the horizon, no double-blind experiments are necessary to prove its efficacy.

What Is Not Obvious

Statistics are useful in orienting us to that which is not obvious. They do not necessarily prove the point, but raise a warning flag that suggests more careful observation of a possible side effect. They warn the physician to be on the lookout. Certainly, if the undesirable side effects of a drug were readily apparent, the practicing physicians would have detected them in the normal course of practice. Once alerted by statistical studies that less obvious side effects might indeed occur, the physician is guided to make a choice between the benefit of the drugs and the potential risk of administering them. Traditionally, physicians have been trained to choose between the risk and benefit of any drug they administer, and the populace, which is not an ass, has been willing to accept this choice. Too often, however, double-blind studies that have maligned certain therapies have never measured the deleterious effects of alternative therapies.

Another factor often ignored by statistics is the sense of well-being of the patient receiving a medication. The question, "How are you feeling?" is a total statistical survey of one patient, and the answer, "Much better," is significant to the nth degree. After all, you can't go into a room full of caged rats and ask, "How are you, fellas?" and expect to get statistically useful information. Thus, the audience to whom a statistic is presented plays a vital role in the usefulness of the statistic.

Hardly a day goes by without erudite prose erupting to show that doctors just do not know what they are doing. The most recent expose was a five-day series in the *New York Times* which used statistics freely to batter an already beleaguered medical profession. When the *Times* presented its recent survey about the damage doctors do, it buttressed its insinuations with reams of supposed statistical studies Many statements that in the aggregate constituted an unwarranted attack on the practicing physician are prefaced with the devastating stopper "... in a double-blind study..." For the doctor, the "statistics" presented by the *Times* simply raised quesions which required careful study or corroboration. To the layman, the articles were a disservice that caused a minor panic. The physician is able to evaluate the material in the light of his personal experience and that of his colleagues; he is able to measure the greater good against the lesser risk. The patient, on the other hand, sees it as an all or none proposition, and wonders whether he is being poisoned.

The science of statistics is great. It is cross-sectional, informative, ingenious, and instantaneous. But it is not necessarily the truth, nor more valid for the individual, than the data accrued over the years by experienced and observant physicians and patients alike who seek to trade the greater good for the calculated risk.

The Absurd Reduction

Recent articles simplistically implying that doctors do more harm than good pose the null hypothesis that there is no difference between doctors and other people with respect to effective practice of medicine, that the profession of medicine is superfluous. If so, the conclusion is an absurd reduction of the medical experience, and an equally absurd reflection of the times we live in and the *Times* we read.

Whom the Gods would destroy, they first make mad; whom governments and the press would destroy, they first malign.

Fibrinogen Assay Aids Detection of 90% Bladder Ca

Medical Tribune Report

BUFFALO—Researchers at Roswell Park Memorial Institute here have achieved a 90% bladder cancer detection rate by supplementing the conventional cytology detection method (which scores only about 70%) with a test for the presence of fibrinogen degradation products (FDPs) not normally present in the urine.

In patients with active bladder cancer, cytology-FDP testing correctly detected the disease in 18 of 20 patients, Dr. Zew Wasjman, a urologist, told MEDICAL TRIBUNE. There were negative results in 46 others with inactive bladder cancer and in 20 controls who neither had a history of bladder cancer nor any other evidence of cancer, Dr. Wasjman said.

Inexpensive Screening

The cytology-FDP tests are inexpensive and could be used in screening programs after further testing on control groups is completed in about a year, he said. The new detection method could have important applications among workers in rubber, chemical, and synthetic dye industries who are already being screened by conventional means because their exposure to aromatic amines means they run a higher risk of bladder cancer.

Exposure to amines and cigarette smoking is partially responsible, most experts agree, for the doubling of the incidence of bladder cancer in the last 10 years. The American Cancer Society estimates that it will claim the lives of 6,600 men and 2,900 women in 1976.

Coinvestigators with Dr. Wasjman were Drs. T. Ming Chu, Claude E. Merrin, and Gerald P. Murphy.

Placental Progesterone May Protect Fetus From Rejection

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that while high placental levels of progesterone provide local immune suppression, progesterone levels are greatly diluted elsewhere in the pregnant woman's body, and thus do not compromise her immune defenses.

In describing the investigation, Dr. Siiteri said his team acted on the hypothesis that progesterone is "nature's immunosuppressant." Earlier efforts to demonstrate this had failed, he said, because the hormone had been administered systemically and thus did not achieve the local concentrations—from 2 to 10 μg/gm—found in the human placenta. The San Francisco group began by seeking to mimic the high levels found in the gravid human uterus.

In a series of rat studies, Dr. Siiteri and his group implanted porous silastic tubes in the animals' flanks. The tubes were wrapped either with cotton thread, "a highly antigenic substance," or with hamster skin. One set of capsules contained progesterone that diffused out into the surrounding tissue; the control set contained no progresterone. The implants were placed in the flank, rather than the uterus, Dr. Siiteri explained, to demonstrate that the hormone's action is not confined to one organ. Some 50 rats were used.

Evidence that progesterone protects fetus against maternal rejection by exerting immunosuppressive effect on placenta may have implications in transplant surgery and treatment of spontaneous abortion. Above, in rats with hamster skin implants, tissue adjacent to progresterone-filled silastic tubes (right) remains viable, with no inflammatory response evident. Empty control tubes (left) become encased in granulomatous tissue; hamster skin below tubes becomes necrotic.

In control animals, the cotton-wrapped implants were, within one week, surrounded by granulomatous tissue and adhesions which anchored them to the underlying fascia, the investigator reported. "In marked contrast, the progesterone-containing capsule elicited little if any inflammatory response and lay free at the site of implantation." In the animals with the hamster skin implants, at 21 days, "Tissue that was adjacent to progesterone-containing capsules remained in a healthy viable state, whereas the control skin was completely destroyed, as expected," Dr. Siiteri said.

On the basis of the observation that high concentrations of progesterone exert anti-inflammatory and immunosuppressive activity, the team studied the hormone's effect in cultures of human mixed lymphocytes, and found that 1-10 μg/ml of progesterone exerted "significant suppression" and 20 μg/ml "virtually complete inhibition" of lymphocyte reactions.

Similar to Glucocorticoids

"The studies thus establish that progesterone, in sufficiently high concentrations, possesses activity similar to that of glucocorticoid hormones which are commonly used to achieve immunosuppression in transplant patients," Dr. Siiteri declared, adding: "Other lines of evidence are consistent with the hypothesis that progesterone provides immunosuppression during pregnancy. A fall in progesterone production occurs in many species near the end of normal gestation."

In an interview, he said that the implications of his group's work have aroused interest in two areas of clinical investigation: one is the possibility that progesterone in high concentrations may be employed to exert a local immunosuppressive effect in organ transplantation without affecting the host's total immune system; the other is the use of progesterone in chronic aborters. Previous attempts to forestall abortion by giving pregnant women progesterone have been unsuccessful, Dr. Siiteri suggested, because systemic administration was employed, thus failing to achieve high local uterine levels. But "new solutions, based on our observations, may help to reduce premature birth, which is a major obstetrical problem," he declared.

Cardiac Arrythmia Deaths Linked to Low Mg Intake

Medical Tribune World Service

MONTREAL—Why do people who live in soft water areas die more often of cardiac arrhythmias than people in hard water areas? Researchers in Ontario are trying to find the answer. A link with water-borne magnesium is suggested.

"As in other parts of the world, death rates from ischemic heart disease in the Province of Ontario show an inverse correlation with the hardness of the local water supply. This relationship has been shown to be due largely to an excess of sudden deaths in the soft water areas—due presumably to an increased tendency to cardiac arrhythmias," Dr. Terence W. Anderson, of the Department of Preventive Medicine and Biostatistics, University of Toronto, told the Second Annual Symposium on Magnesium.

"The evidence in Ontario suggests that a water factor is operative here. The actual number of infarctions is probably not greatly different in the various regions. What is different is a tendency to go into abnormal rhythms and sudden death," he said.

"Magnesium deficiency is known to produce neuromuscular irritability. We have investigated the possibility that residents of soft water areas have less magnesium in the myocardium than residents in hard water areas."

The research described by Dr. Anderson has been going on for several years. Ontario is a province where water varies considerably, from very soft to very hard. Their earlier findings in two cities confirmed that the percentage of sudden deaths following arrhythmias was higher in soft than in hard water cities, and that held true right across the age range in males and females.

"This was not attributable to it being easier to get to hospital in one city than another. The two cities had similar facilities. In fact, a higher percentage of arrhythmic deaths persisted after the patients were admitted to hospital."

Their study then looked principally at calcium and magnesium serum levels in subjects in the two areas—calcium and magnesium being water's major trace elements—but no difference was found in serum samples.

However, calcium and magnesium behave differently in the body. While calcium is found predominantly in blood serum, magnesium stays mainly inside muscle cells, especially in heart muscle where it plays a vital role related to the heart's energy requirements, Dr. Anderson explained.

Autopsy Studies

A further line of attack therefore was comparative and involved autopsy studies done on accident victims and heart attack victims in soft and hard water areas. Comparisons between heart muscle taken from heart attack victims and from the presumably healthy accident victims in the soft water area showed the difference.

"The comparison confirmed low levels of myocardium magnesium in victims of heart attacks with a mean value of 22% lower than in the corresponding value in accidental deaths."

Highly refined North American diets, Dr. Anderson pointed out, may be magnesium deficient.

"It would appear that in Ontario at least, the contribution of water-borne magnesium to total dietary intake may be critical; that some residents of soft-water areas are in a state of subclinical magnesium deficiency. If these individuals suffer a myocardial infarction, they may then be at increased risk of developing a fatal cardiac arrhythmia."

Negative Chest-Wall Pressure Aids Ca Patients' Pneumonia Survival

By MICHAEL HERRING
Medical Tribune Staff

NEW ORLEANS—Ten out of 14 young, immunosuppressed, cancer patients have survived acute episodes of "diffuse pneumonia" with the help of continuous negative chest-wall pressure (CNP) therapy, a new means of improving arterial oxygenation in hypoxia.

In addition to helping achieve the high survival rates for this formidable complication, "CNP therapy eliminates the need for endotracheal intubation and prolonged use of muscle relaxants and sedatives, and permits an early reduction in oxygen concentrations, thus minizing the hazard of pulmonary oxygen toxicity," Dr. Shyamal K. Sanyal told a recent meeting here of the American Lung Association.

All the children (six months to 14 years of age) had progressive bilateral alveolar disease caused by Pneumocystis carinii infection, with respiratory distress and, in all but one case, fever, reported Dr. Sanyal, who is Director of the intensive care unit and Chief of the cardiopulmonary disease service at St. Jude's Children's Research Hospital in Memphis.

O_2 Given to All

"Either pentamidine isethionate or trimethoprim-sulfamethoxazole as well as chlorpheniramine, intravenous fluids, and oxygen were administered to all patients," he added.

As respiratory distress progressed, the patients were placed "in an Emerson tank respirator without bellows, and hooked up to a source of continuous negative pressure," Dr. Sanyal said in an interview. With this pressure constantly applied outwards, "the response [of the lungs] involves recruitment of nonventilated alveoli or progressive overdistention of these structures."

When more alveoli are brought into action by CNP, arterial oxygen is remarkably improved, as in the ten patients, he noted. However, alveolar overdistention could lead to compromised lung compliance and a pulmonary air leak, as in the four who died, Dr. Sanyal cautioned. The possibility of an "optimal pressure" for CNP therapy should be investigated, he said.

While the exact mechanism of action in CNP is not clear, he added, an increase in vascular transmural pressure caused by the continous negative pressure could increase pulmonary blood flow by decreasing pulmonary vascular resistance and serve to explain the enhanced arterial blood oxygenation.

His coworkers, also at the hospital, included Thomas L. Avery, PhD., and Drs. Mohinder K. Thapar, Walter T. Hughes, and Scott Harris, all in the department of cardiopulmonary services.

IN CONSULTATION

What's New and Important About Serum Alpha$_1$-Antitrypsin in Man?

The Consultant

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IT IS 12 YEARS since Laurell and Erikson first described a strong association between severe alpha$_1$-antitrypsin deficiency and chronic obstructive pulmonary disease of unusually early onset. Ten years ago, Fagerhol and Laurell first recognized the genetic heterogeneity of the alpha$_1$-antitrypsin; currently, well over 20 different alleles for alpha$_1$-antitrypsin have been described. These alleles appear to regulate the serum level of the protein, as well as its electrophoretic mobility. The system of alpha$_1$-antitrypsin alleles is termed the *Pi* system (protease inhibitor). Normal individuals are of Pi type M, and those with severe deficiency are of Pi type Z. The latter have a slow-moving alpha$_1$-antitrypsin on electrophoresis, in an amount only 10-20% of normal. Several recent studies have demonstrated that alpha$_1$-antitrypsin is stored in a primitive molecular form in discrete globules in the liver cell cytoplasm of Pi type Z individuals.

The striking high frequency of carriers of the Pi type Z gene (2.5% of most populations) means that 1/1600 to 1/4000 individuals is homozygous Pi type Z. Clinical correlates of Pi type Z include infantile liver disease, often progressing to cirrhosis, the onset of panlobular emphysema in young adult life, or, rarely, a combination of these.

Very recent studies suggest that the structural difference between Pi type Z and Pi type M alpha$_1$-antitrypsin may consist of one or two simple amino acid substitutions.

What is the source of serum alpha$_1$-antitrypsin in man and what determines the amount and circulating properties of this protein?

Serum alpha$_1$-antitrypsin is synthesized in the liver cell and rapidly secreted into serum in the normal, Pi type M, individual. Pi type Z alpha$_1$-antitrypsin is made in the liver cell, partially secreted into serum in very low amounts, and excessively stored in the liver cell cytoplasm. The circulating levels and electrophoretic mobility of alpha$_1$-antitrypsin are determined by the genetics of the protein. In addition, a variety of drugs (estrogens, for example) and non-specific inflammatory states can induce an increased rate of synthesis of alpha$_1$-antitrypsin by the liver, resulting in elevated circulating levels of the protein.

What clinical entities are associated with a deficiency of alpha$_1$-antitrypsin?

Hereditary alpha$_1$-antitrypsin deficiency may be associated with liver disease beginning in infancy, with panlobular emphysema beginning in young adult life, or, rarely, with a combination of the two diseases in childhood. Replacement therapy with alpha$_1$-antitrypsin deficiency is characteristic of infants with the respiratory distress syndrome. This is not on a genetic basis, and is accompanied by deposits of alpha$_1$-antitrypsin in the alveolar hyaline membranes.

Does the degree of deficiency of alpha$_1$-antitrypsin affect the type of clinical entity that develops?

Yes, as noted above, severe alpha$_1$-antitrypsin deficiency of Pi type Z is clearly associated with lung and/or liver disease. The carrier state, Pi type MZ, may be associated with lung or liver disease in occasional patients, but does not clearly predispose an individual to clinical disease of any kind. However, it has been-documented that lung function in Pi type MZ individuals deteriorates more rapidly with age than it does in a normal Pi type M person.

Is there any type of treatment that can be used to alter this condition once it has been recognized?

There is currently no specific means of elevating genetically low alpha$_1$-antitrypsin levels. It would be impractical at the present time to consider replacement with normal human alpha$_1$-antitrypsin, since the half-life of the protein in the circulation is only four to six days. General principles of comprehensive clinical care for pulmonary and/or liver disease should be applied. Prohibition of smoking is an important adjunct to the treatment of Pi type Z individuals, once the condition has been recognized, since smoking has definitely been shown to hasten the pulmonary damage in the disease. It is hoped that synthetic enzyme inhibitors will become available for the treatment of this condition some day.

Pediatrician Finds Early Snuggling To Mother Is Good for Neonates

Medical Tribune Report

ST. LOUIS—Babies who spend the first 45 minutes of life snuggled skin-to-skin against their mothers have less chance of early infection, more weight gain in the first year, and a longer period of breastfeeding than infants who are separated from their mothers during the first 24 hours, Dr. John Kennell said here.

Addressing a subspecialty session at the American Pediatric Society meeting, Dr. Kennell, Professor of Pediatrics at Case Western Reserve University Medical School, Cleveland, also reported on a related study of 60 mother-infant pairs, which revealed that "those mothers given early contact were significantly more affectionate with their babies than the delayed contact or the control mothers."

Both studies, he said, suggest that "close contact for the mother and her infant during the first minutes and hours after birth may be crucial for the formation of a strong attachment," which greatly influences the child's health. The studies also support previous findings that there is a sensitive period "when both mother and infant appear to be highly aroused."

The present findings, he added, "begin to define the short duration of the sensitive period and emphasize that just 45 minutes of early contact may have more profound effects than we previously appreciated. These findings compel the reconsideration of hospital practices that even briefly separate mother and infant," he stressed.

Dr. Kennell's research team, including Dr. Marshall Klaus, also Professor of Pediatrics at Case, based their findings on 40 mother-infant pairs at the Social Security Hospital in Guatemala.

"The 20 control mothers were separated from their infants from the time of delivery until the first feeding at 24 hours, as is routine at this hospital," he said.

"The 20 early-contact mothers . . . spent 45 minutes after the episiotomy repair, alone, skin-to-skin, in a private room with their undressed infants under a heated panel where they were encouraged to breast feed." Other than this, care of mothers and infants was identical, he added, with free powdered milk available to all during the first year.

Follow-up visits at one, three, six, nine, and 12 months showed that "the infants whose mothers had early contact gained significantly more weight . . . and also had fewer infections," Dr. Kennell reported. In addition, while all were breastfeeding at the time of discharge, "the percentage of early contact mothers who were still breastfeeding was significantly greater than the control group at six and 12 months (196 vs. 104 days)."

To investigate the duration of the "sensitive period," the research team took a fourth sample of 60 primiparous Guatemalan mothers and divided them into three groups: early contact (immediately after birth), delayed contact (after 12 hours), and control (after 24 hours). By carefully observing mother-infant interaction 36 hours after birth, researchers scored the mothers on specific points of affectionate behavior (e.g., talking, fondling, kissing, smiling, face-to-face contact) during the first 15 seconds of each minute for 15 minutes. Again, the early-contact mothers were significantly more affectionate with their babies than the other two groups.

Next In Consultation

DR. JOHN F. GRIFFITH, Professor and Chairman, Department of Pediatrics, University of Tennessee Center for Health Sciences, and Medical Director, Le Bonheur Children's Hospital, Memphis, Tenn., will discuss "slow virus" infections in children, whether administration of live-virus vaccines to infants may result in an increase in subacute sclerosing panencephalitis, the pathogenesis of herpes simplex virus infections, treatment of "slow" virus infections, and signs of such infections that a general practitioner should look for.

Early Trial Finds Dicyclomine Eases Signs of Achalasia

Medical Tribune Report

MIAMI BEACH—An oral anticholinergic agent has relieved the symptoms of achalasia in an early controlled trial, a Temple University team has reported.

Difficulties in swallowing solids and liquids were "significantly improved", and such symptoms as regurgitation and vomiting were relieved to a lesser extent, in almost all patients who received dicyclomine HCl orally or subcutaneously in the course of a 14-week, double-blind crossover study, the team told the American Gastroenterological Association.

The findings point to the possibility of a useful role for anticholinergic therapy in symptomatic achalasia, and warrant larger controlled trials and follow-up studies, said Dr. Ira F. Lobis, Temple Research Fellow.

The study was prompted by the observation that anticholinergic drugs inhibit the activity of both gastrin and cholinergic stimuli at the level of the lower esophageal sphincter (LES), Dr. Lobis explained. Since achalasia is attributed to functional obstruction of the distal esophagus produced by an abnormal LES, he said, it seemed useful to try a pharmacologic approach, prior to conventional mechanical procedures to treat the disorder.

Ten patients with achalasia were entered in the study and the effect of dicyclomine on their LES pressures was measured serially to establish baseline data. The patients were then randomized into a blind crossover trial, with dicyclomine 20 mg or placebo administered for four weeks, followed by crossover therapy for four weeks, no treatment for two weeks, and resumption of therapy for an additional four weeks.

After subcutaneous administration of the anticholinergic, LES pressures dropped maximally from a basal level of 44 to 25.4 mm Hg, and after oral administration the pressures dropped from 41.9 to 28.5 mm Hg, Dr. Lobis reported.

In an interview, Dr. Lobis stressed that anticholinergic therapy is not designed to replace conventional methods, but "may reduce symptoms long enough to delay surgery, and may have a valuable role in the overall therapy of patients with achalasia." Coauthor was Dr. R. S. Fisher.

Tumor-Specific Antigen Aids Recovery from Lung Cancer

Continued from page 1

of cancer with important implications for immunodiagnosis and immunotherapy."

The clinicians report that of 26 lung cancer patients treated post-surgically with immunotherapy or immunotherapy plus chemotherapy all are alive and 24 are disease-free, half of them for more than 21 months. Among a control group of 23 patients treated by standard means, six have died.

The new factor in the treatment strategy is an allogeneic, tumor-specific antigen, developed and prepared by Dr. Hollinshead in Washington and used clinically by Dr. Stewart in Ottawa. Despite the modest number of patients and the preliminary nature of the study, the investigators are cautiously hopeful that their work will lead to a better prognosis for lung cancer patients, 40-50% of whom now die from recurrent disease within two years after surgery, they told MEDICAL TRIBUNE in an interview.

Beginning of New Era

Dr. Stewart and Dr. Hollinshead, who have been collaborating in the project since 1969, see their achievement as the beginning of a new era in the treatment of all types of tumors. "We admit that this is a very small series, but we do feel that the preliminary results suggest the immunochemotherapy approach might well be applicable to other tumor systems," Dr. Stewart said.

After surgery, Drs. Stewart and Harris treated each patient who received immunochemotherapy with methotrexate, then "rescued" the patient from the toxicity of the massive dose of MTX with citrovorum factor. The procedure is repeated 30 days and 60 days later. Seven to nine days after each course of MTX and citrovorum factor, the patient receives an IM injection of tumor antigen, derived from tumor cells of the same histologic type as his own combined with Freund's complete adjuvant. Each of the three doses contains between .521 mg and 1 mg of antigen, depending on the patient and the availability of antigen, for a total of about 1.5 mg.

Dr. Stewart believes that the chemotherapy and immunization enhance each other's effectiveness, and plotted his clinical strategy to make the most of this synergistic interaction.

'Rebound Overshoot'

Methotrexate suppresses the ability of the bone marrow to produce lymphocytes. "After rescue with citrovorum factor, however, the immune system not only recovers, it comes back even stronger than before," said Dr. Harris, who calls the phenomenon "rebound overshoot." At this point, the tumor antigen is given in order to equip the new army of lymphocytes, recruited by the methotrexate, with weapons specifically lethal to tumor cells.

The patients tolerated the vaccine well, although all of them developed ulcers at the vaccination site, most of which became infected. Staphylococcus aureus caused most of the infections, which responded well to antibiotics and healed completely within 12 months. In seven patients, high fever (up to 40° C) followed the second injection of the vaccine. The fever lasted less than 30 hours and required no treatment beyond bed rest and aspirin.

The investigators emphasized that their work, which they presented at the recent meeting of the American Society of Clinical Oncologists in Toronto, is still experimental and cannot at present be applied to large numbers of patients. The sheer logistics involved complicate the picture further.

Continued in the next issue

In her lab at George Washington University Medical Center, Ariel C. Hollinshead, Ph.D., elected "Medical Woman of the Year" for her "pioneer work," adjusts microconcentrators during final purification of lung cancer vaccine.

from France

'Liver Attack' in Frenchmen Held Nonexistent

Continued from page 2

these disturbances, lasting from a few hours to two or three days, may be triggered by such factors as alcoholic excesses or food intolerance—but the liver is blamed. It is also blamed for everyday tensions.

Dr. Benhamou also pointed out that in France there is an extreme tendency to blame the liver for symptoms as varied as cutaneous eruptions, isolated headaches, or any digestive disorder, all of which are irrelevant in hepatic pathology. A systematic exploration of the liver and bile ducts in patients with these symptoms reveals no anomaly, even with the most sensitive tests. And patients suffering from real illness of the liver, associated with a major deterioration of hepatic functions, such as chronic hepatitis or certain cirrhoses, never complain of these symptoms so widely attributed to the liver.

In many cases the precise cause of the patient's "liver ailment" may be detected. Migraine headaches, for example, are related to a vasomotor phenomena, not the liver, and they may be associated with vomiting, frequently the primary symptom. Their treatment, particularly with ergotamine derivatives, is often very effective—but this has nothing to do with the liver.

Right subcostal pains may be related to many different causes, such as cholelithiasis, duodenal ulcer, or colic. Similarly, intolerance to certain foods is often accompanied by digestive reactions, such as nausea, vomiting, diarrhea—the origin of which is gastric and intestinal, not hepatic.

It may happen that the origin of the symptoms remains unknown, said the French hepatologists, but there is too much haste on the part of patients and physicians to blame the liver without proof. The abuse of medications is often habitual in such patients, leading to iatrogenic pathology. Cessation of drug taking alone may lead to a spectacular regression of the "liver attack" in a substantial number of cases.

The "liver attack," said Prof. Dhumeaux, is a convenient diagnosis, with which the patient is readily satisfied even though the real cause of the symptoms may then be ignored.

from Britain

MDs Advised to Look for Scurvy In 'Gout' Patients

Continued from page 2

treatment, it is arguable as to what extent maintaining normal uric acid levels will help renal function.

In the case of asymptomatic hyperuricaemia, now more commonly seen since the advent of autoanalysers, his advice is not to rush into treatment.

With serum uric acid levels of 8-8.9 mg per 100 ml, only about 25% of men turn out to have gout. This proportion jumps to 90% with serum uric acid levels of more than 9.0 mg %.

The risks to be considered when faced with a patient with asymptomatic hyperuricaemia are gout (which is nothing to worry about till the first symptoms appear), renal damage, and ischaemic heart disease.

Little is known about the likelihood of an asymptomatic hyperuricaemic patient developing either renal impairment or ischemic heart disease.

A mild renal impairment is common in gout patients but it is a case of which is the cart and which the horse. There is, of course, the possibility of uric acid stones, Dr. Scott concluded.

from Japan

Protection Urged For Fingertips of Isotope Workers

Continued from page 2

for 13 weeks without protection, thereby exceeding the maximum digital exposure tolerance dose of 20 rems.

● More recently, a questionnaire circulated among some members—those over 40 years of age—of the Society of Medicorradiation and the Society of Clinical Radiation Technicians disclosed smooth finger tips and other anomalies in 24% of the physician group and 17% of the technicians. A follow-up study of fingerprints in 102 responding physicians showed 3.9% to have a greater number of wrinkles and shallower furrows than normal fingerprints (see photo).

In radiologic practice, acute disorders due to exposure rarely occur, Dr. Koga said. The commonly encountered disorders seem to be those that develop more slowly; cutaneous atrophy, leukemia, cancer, cataracts, premature aging, and shortened life expectancy.

Back in 1970, it was estimated that only about 0.3% of medical, paramedical and dental personnel in Japan were occupationally exposed to more than 5 rads, Dr. Koga said. Although this figure has remained more or less unchanged over the intervening years, there is some evidence that the actual exposure level may be higher.

Dr. Koga concluded that hands and fingertips may be especially vulnerable to possible radiation hazards, particularly with the increasing clinical use of isotopes, such as 99MTC, which have a short half-life period.

The Only Independent Weekly Medical Newspaper in the U.S.

Medical Tribune

and Medical News

Published by Medical Tribune, Inc.

Action on the Potential Swine Flu Epidemic...

THE THREAT of swine influenza has precipitated action by the President of the United States, HEW and its advisory bodies, and by Congress. "Swine flu" poses problems of hard decisions mandatory for those responsible for the national health. Beyond the mechanics of logistics, it raises legal as well as ethical and medical issues. It demonstrates the extent to which judgments are absolutely essential in the fight against disease. It has also provided, we believe, an exemplar par excellence of double or multiple standards as they exist in government actions on health. All this is the consequence of one death, that of an 18-year-old recruit at Fort Dix.*

Let us agree that for "government" to have done nothing in respect to a flu epidemic threat would have been irresponsible and reckless. But let us also compare from a total public health perspective the manner in which the program to combat a potential epidemic has been carried out and the contrast it presents to the endless delays and rigidities imposed by the FDA in respect to new therapeutic agents of even greater importance.

A case in point is the very real, existing "epidemic" of hypertension to which 25 million Americans are exposed—year in and year out—to the crippling morbidity of strokes and the high mortality of cardiovascular damage. Despite an impressive weight of medical opinion, for many years the FDA has held back approval of effective new drugs on the grounds that its actions would breach the very regulations which, as we note here, seem to have been "thrown to the winds."

Accepting as a premise the governmental decision to vaccinate 200 million Americans as valid and that everyone has acted in good faith, let us examine all the implications that follow:

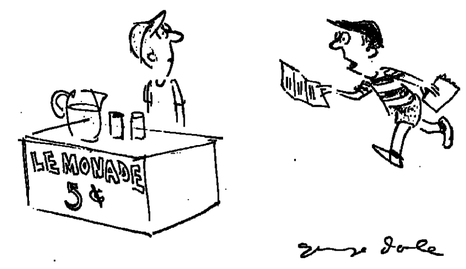
1. What hard experimental and clinical data was available on the acute and chronic toxicity of the specific "swine flu" vaccine which virtually all Americans are supposed to receive?
2. Some virdses are related to cancer and teratogenicity. Have carcinogenicity and teratogenicity studies similar to those required for drugs been carried out?
3. What about reports that prisoners will participate in the screening program? How does this comport with recent complaints that such volunteers should not participate in drug research?
4. Will true "full disclosure" truly inform the general public both as to the chances of the epidemic occurring, the extent of its dangers, or the efficacy of the vaccine and its potential side-effects?
5. What is the morality of vaccinating every person in a population to prevent a pandemic whose potential threat would be primarily to the elderly and high risk groups?
6. What about the "long-term follow-up" currently under consideration for other experimental medications? In view of the scope and the unanswered questions indicated above, what plans have been made for such monitoring of this unique national experiment?

Let us be absolutely clear. We do not believe that the issues we raise rule out the necessity for responsible government action to head off a swine flu epidemic. Some of us would have preferred to see the swine flu vaccine prepared so as to be available, plans made to innoculate high risk groups and then a reserve program to extend protection depending on developing circumstances. We do not, despite such differences in opinion, fault either the President, the Assistant Secretary for Health, or Congress. We believe that all, including HEW, the White House Office of Management and Budget, the Domestic Council and the advisory bodies of scientists (who included such outstanding experts as Sabin, Salk, Kilbourne and Davenport) have acted in good faith and proposed a program predicated on the limited information available in accord with their best judgments.

What is astonishing is the relatively limited discussion of all these relevant, valid issues either in Congressional hearings, in press editorials, or by the usual TV commentators. One would hope that if an epidemic does not occur that those who have had nothing to say to date on these points will have the decency to recognize their present silence after attaining 20-20 hindsight. It is easy to throw bricks at people in glass houses but very difficult to have to face the necessity of judgments relating to life and death—yourself.

The more imperative lesson to be learned from all this is the need for a new look at the dogma and rituals which have grown up in respect to the development and clearance of new therapeutic agents. We refer particularly to the virtually absolute rejection of expert opinion and judgment and even the practical exclusion of experiments of substantial evidence for efficacy, except for double-blinds, which are being applied even to new major life-saving medications.

**The recruit was seen in the dispensary and then assigned to his quarters for 48 hours. He left his bed before then to join a forced march at night with the other recruits. Lagging behind, despite frequent rests, he eventually collapsed, was rushed to hospital where he died shortly thereafter.*



"It's a nasty letter from the Pure Food and Drug people."

...and Inaction Based on a Double Standard

THE LIKELIHOOD of a U.S. swine influenza epidemic in 1976-77 is estimated in a range from a low of 2% to a "probability of 10 percent, 35 percent, and less than even" (*Science*, May 14, 1976). Our epidemic of heart disease, both in respect to incidence and death, is very, very real—it exists now. It occurs not once every 50 years but year in and year out. The Assistant Secretary for Health, Dr. Theodore Cooper, has publicly recognized coronary and hypertensive heart disease as a national epidemic. There are over 750,000 American cardiovascular deaths annually. Compare this to "the 1918-19 pandemic which swept around the world . . . in successive waves [and] killed 548,000 Americans of all ages" (*Science*, May 14, 1976).

Despite this, not only are judgmental decisions rejected but significant data on efficacy of therapies, dosages, chronic toxicities and patient salvage, which are available, are disregarded in respect to critical new cardiovascular medicines. Certainly the use of beta-blockers to the extent of several tons per month in Britain alone affords some assurance of safety as well as a body of experience in respect to efficacy. A range of life-saving beta-blockers available in such medically sophisticated and therapeutically monitored societies as Sweden and Great Britain has been denied U.S. doctors and patients for years—and continues to be held back. The flu vaccine situation should stand as a warning that when scientific decisions are left primarily or solely to the government, double or different standards can quickly prevail. The situation reinforces the conviction that in areas of medicine and health open debate must be preserved and government nonpartisanship and true objectivity must be a *sine qua non* of a democratic society.

The contrast between what the government says and what the government does is bewildering. Is not the time long past when government can, as it wishes, justify inaction on the basis of those very criteria which it rejects or disregards in respect to its own actions?

LETTERS TO TRIBUNE

Legally Speaking

Your editorial [MT, June 23], on the American Association of Trial Lawyers effort to bar the Medical Society of the State of New York from what it attempted to call "false advertising" when the Medical Society used an advertising supplement in New York State newspapers, has prompted me to respond.

The Society favored pending legislation which placed a ceiling on contingency fees and which would limit awards for pain and suffering. The Society also called the McGill Commission's report "impartial." According to the lawyers' association's standards, the Commission was not impartial since "five of the nine members of the Commission were at one time directly or indirectly connected with the medical profession and providers of health care."

The lawyers' association, when it petitioned the Federal Trade Commission, stated that the Society's advertising could be condemned for calling the McGill Commission "impartial." Where is the evidence for this? Does a man's association with the medical profession make him incapable of impartiality? The answer to this question lies in the realm of intuition. Facts must be proven by other facts. Where are the Association's facts?

Supposing the Association, and not Governor Carey, would be given the responsibility of creating a Commission. Would they appoint lawyers to the Commission or engineers or housewives? The New York State Legislature is composed, in the majority, of lawyers. Are they incapable of impartiality?

The Association's procedural attack points up an irreconcilable difference in the thinking of doctors and lawyers. Had the positions been reversed, would a group of doctors have attacked the substantive aspects of the report rather than the composition of the Commission?

GEORGE A. FRIEDMAN, M.D., J.D., LL.M.
Fellow,
American College of Legal Medicine

Ismelin® sulfate
(guanethidine sulfate)

Esimil®

guanethidine monosulfate	10 mg
hydrochlorothiazide	25 mg

WARNING
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

INDICATIONS
Ismelin
Moderate and severe hypertension either alone or as an adjunct.
Esimil
Hypertension. (See box warning above.)

CONTRAINDICATIONS
Guanethidine: Known or suspected pheochromocytoma; hypersensitivity; frank congestive heart failure not due to hypertension; use of MAO inhibitors.
Hydrochlorothiazide: Anuria; hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS
Antihypertensives are potent drugs and can lead to disturbing and serious clinical problems. Physicians should be familiar with all drugs and their combinations before prescribing, and patients should be warned not to deviate from instructions.

Guanethidine

Warn patients about the potential hazard of orthostatic hypotension, which can occur frequently and is most marked in the morning and is accentuated by hot weather, alcohol, or exercise. To help prevent fainting, warn patients to sit or lie down with onset of dizziness or weakness, which may be particularly bothersome during the initial period of dosage adjustment and with postural changes. The potential occurrence of these symptoms may require alteration of previous daily activity. Caution patients to avoid sudden or prolonged standing or exercise while taking the drug.

Concurrent use with rauwolfia derivatives may cause excessive postural hypotension, bradycardia, and mental depression.
If possible, withdraw therapy 2 weeks prior to surgery to reduce the possibility of vascular collapse and cardiac arrest during anesthesia. If emergency surgery is indicated, administer preanesthetic and anesthetic agents cautiously in reduced dosage and have oxygen, atropine, vasopressors, and IV solutions ready for immediate use to treat vascular collapse. Vasopressors should be used with extreme caution in patients on guanethidine because of the possibility of augmented response and the greater propensity for cardiac arrhythmias.
Dosage requirements may be reduced in presence of fever. Exercise special care when treating patients with a history of bronchial asthma, since their condition may be aggravated.
Hydrochlorothiazide
Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.
Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.
Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.
Usage in Pregnancy
Guanethidine: The safety of guanethidine for use in pregnancy has not been established; therefore, this drug should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.
Hydrochlorothiazide: Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against the possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.
Nursing Mothers
Thiazides cross the placental barrier and appear in cord blood and breast milk.

PRECAUTIONS
Guanethidine: The effects of guanethidine are cumulative over long periods. Initial doses should be small and increased gradually by small increments. Use very cautiously in hypertensives with renal disease and nitrogen retention or failing BUN levels; coronary disease with insufficiency or recent myocardial infarction; cerebral vascular disease, especially with thrombosis. Do not give guanethidine to patients with severe cardiac failure except with extreme caution.
In incipient cardiac decompensation weight gain or edema may be averted by the administration of a thiazide.
Remember that both digitalis and guanethidine slow the heart rate.
Peptic ulcers or other chronic disorders may be aggravated by a relative increase in parasympathetic tone.
Amphetamine-like compounds, stimulants (eg, ephedrine, methylphenidate), tricyclic antidepressants (eg, amitriptyline), imipramine, desipramine) and other psychopharmacologic agents (eg, phenothiazines and related compounds), and oral contraceptives may reduce the hypotensive effect of guanethidine. Discontinue MAO inhibitors for at least one week before starting guanethidine.
Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, and hypokalemia). Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance such as nausea or vomiting.
Hypokalemia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe cirrhosis is present, or during concomitant administration of steroids or ACTH.
Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver diseases or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is restriction of salt rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In clinical salt depletion, appropriate replacement is the therapy of choice.
Impotent elevations in plasma calcium may occur in patients receiving thiazides, particularly in those with hyperparathyroidism. Pathological changes in the parathyroid gland have been reported in a few patients on prolonged thiazide therapy.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes may become manifest during thiazide administration.
Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS
Guanethidine: Frequent reactions due to sympathetic blockade—dizziness, weakness, lassitude, syncope. *Frequent reactions due to unopposed parasympathetic activity*—bradycardia, increase in bowel movements, diarrhea (may be severe and necessitate discontinuance of the drug).
Other common reactions—inhibition of ejaculation, fluid retention, edema, congestive heart failure. *Other less common reactions*—dyspnea, fatigue, nausea, vomiting, nocturia, urinary incontinence, dermatitis, scalp hair alopecia, jaundice (intrahepatic cholestatic), pancreatitis. *Central Nervous System*—dizziness, vertigo, headache, a few instances of anemia, thrombocytopenia and leukopenia have been reported.
Hydrochlorothiazide: Gastrointestinal—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic), pancreatitis. *Central Nervous System*—dizziness, vertigo,

(Brief prescribing information continued on next page)

CIBA

in moderate hypertension.

"...most patients tolerate guanethidine with minimal side effects, when dosage adjustment is carefully managed."[1]

1. Freis ED: *The Modern Manag... ment of Hypertension*, US Gover... ment Printing Office, 1973, pp 13, 1...

Currently, there is a positive trend towards reevaluating Ismelin (guanethidine) for use in moderate hypertension.

Perhaps the most effective antihypertensive available, Ismelin offers convenient, once-a-day dosage—a major factor in encouraging patient compliance.

And, when given in moderated dosage, guanethidine does not appear to present a major side effect problem.[1-3]

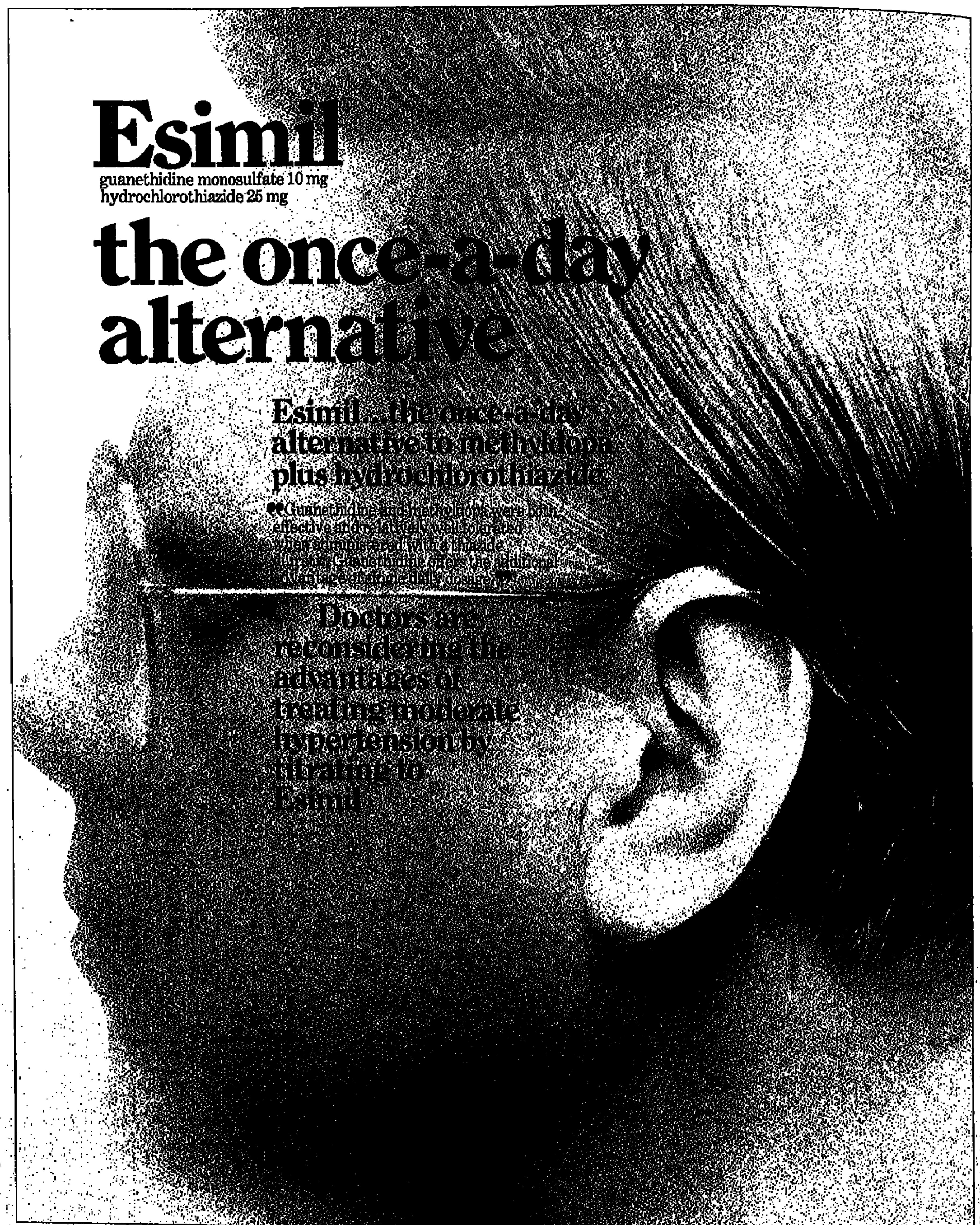
When Ismelin is added to other antihypertensives, initial doses should be small and increased gradually by small increments. Once blood pressure control is achieved, all drug dosages should be reduced to lowest effective level, often minimizing side effects.

Patients should be warned about the possibility of orthostatic hypotension and cautioned to avoid sudden or prolonged standing or exercise.

Please turn page for another option in treating moderate hypertension...

Doctors are rediscovering...

once-a-day Ismelin® (guanethidine)



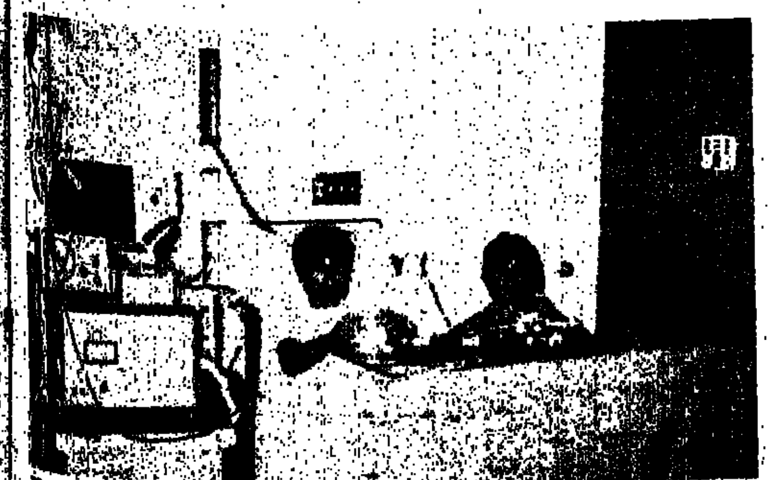

[...]lysis unit is staffed around clock by a pediatric ne[...]ologist and two RNs. On duty here (l. to r.): Sheryl Melber, Children's Hospital, Detroit; Liz Agilpay, Mt. Sinai Hospital, N.Y.C.; Dr. George Schwartz, Einstein.

Only Camping Program For Children on Dialysis Now in Its Second Year

YOUNGSTERS with kidney failure can be like "other kids" and go off to summer camp at a facility equipped with a four-bed dialysis unit at Frost Valley YMCA camp in Oliverea, N.Y. Opened last year and so far the only one of its kind, the camp operates as a satellite of the Hospital of the Albert Einstein College of Medicine in New York. Dr. Ira Greifer, Director of Pediatrics and of the Children's Kidney Center of the Hospital, says the innovative program enables children aged 7 to 16 on maintenance dialysis to enjoy a two-week normal camping experience unavailable before.


Horseback riding ranks high among the favorite outdoor activities available during the eight-week program, which has an enrollment this summer of 32 children.


Each child undergoes dialysis three times a week, with the four- to five-hour procedure fitted as unobtrusively as possible into the schedule of camp-life activities and social contacts.


Hours on dialysis seem shorter with a friend around. This year, program has added a week for children under 7 with their parents.

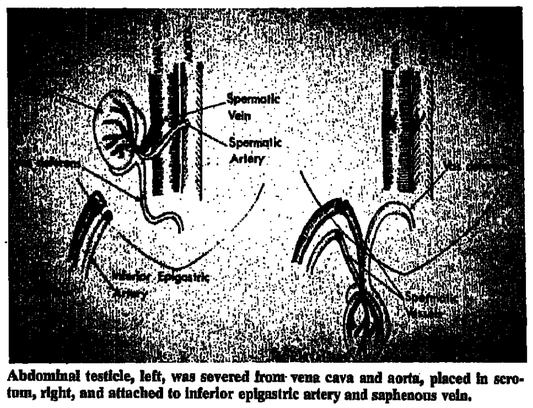

Companionship with others having the same disease—and similar problems—is big plus for young dialysis patients who usually meet each other only in hospital or clinic setting.

Microsurgery Successful in Testis Autotransplant

Medical Tribune Report

PHILADELPHIA—In what is believed to be the first successful operation of its kind, an intra-abdominal testis in a nine-year-old boy has been transplanted to the scrotum using a microvascular surgical technique, a San Francisco urologist reported here. "Although the long-term results regarding fertility will not be known for many years, the immediate results appear good," Dr. Sherman J. Silber told a seminar of the International Society of Pediatric Urologists.

"No testicular atrophy is detectable on palpation," Dr. Silber said. "Good pulsation was noted immediately in the spermatic artery, and venous drainage was excellent. Without microvascular orchidepexy, the testis would have been removed or allowed to remain in the abdomen, where an occult neoplasm might have developed. With our technique, a viable testis was preserved in a position favorable for future observation."



Abdominal testicle, left, was severed from vena cava and aorta, placed in scrotum, right, and attached to inferior epigastric artery and saphenous vein.

Reversed Vasectomies

Dr. Silber, who last year reported a 60% success rate in a new microsurgical technique for reversing vasectomies (MT, Nov. 19, 1975), is Associate Professor of Urology at the University of California, San Francisco, and Chief of Urology at the Veterans Administration Hospital there. His associate and coauthor both in the vasectomy reversals and in this testicular autotransplant has been Dr. Justin Kelly, of Royal Children's Hospital, Melbourne, Australia.

"One to 5% of cryptorchid testes are intra-abdominal and cannot be properly brought down into the scrotum by conventional methods," Dr. Silber said. "In such cases, necessary division of the spermatic vessels results in risk of testicular ischemia. We attempted to solve this problem by microanastomosis of the spermatic vessels to the inferior epigastric vessels in the groin." The autotransplant procedure not only allowed tension-free placement of the high testis, originally located just below the kidneys, into the scrotum, but also provided an adequate blood supply.

This experience with testicular autotransplantation suggests that the microsurgical technique may be applicable in the transplantation of testes from one individual to another, Dr. Silber told MEDICAL TRIBUNE. "Now that it's been shown that the blood vessels can be rejoined, and that reversal of vasectomy has been perfected—these are the only three hook-ups you need—it is going to be very easy to transplant a human testicle and preserve its function.

"One indication would be where the male is infertile and his religious beliefs prohibit artificial insemination," he said, adding that this may apply to Moslems and Orthodox Jews.

"Another indication would be for a man who lost his testes in an accident or was born anorchid, who might seek a transplant instead of going on male hormones for the rest of his life.

"This is an interesting speculation—but it hasn't been done yet," Dr. Silber concluded.

Low Cardiac Output May Resemble Hepatitis

By NATHAN HORWITZ
Medical Tribune Staff

MIAMI BEACH—A lesion that presents clinically as hepatitis but is, in fact, due to low cardiac output stemming from left-sided heart failure, was described here by a Boston team.

The syndrome, which occurs without pulmonary congestion, may not be uncommon in patients with low cardiac output, the investigators suggested.

The new entity was identified in five individuals who had neither hypotension nor right-sided congestive heart failure—well-documented links to overt liver disease, said Dr. J. A. Cohen of the New England Medical Center Hospital.

Hepatitis was initially suspected in the five patients because of anorexia, nausea, and fatigue in two cases and "striking" unexplained transaminase elevations in three, Dr. Cohen told the American Association for the Study of Liver Diseases. Each of the patients had a history of heart disease, but an experienced cardiologist described each, after examination, "as well compensated and without signs of congestive failure." And, said Dr. Cohen, "The cardiologist concluded that the liver dysfunction was unrelated to the heart disease."

Decrease Documented

Liver biopsy in all patients revealed central liver necrosis, but in none was there histologic evidence of hepatitis or of passive congestion. The hepatitis surface antigen was negative in the three patients in whom it was tested, the investigator continued. There was no neck vein distension in the group, and peripheral and central venous pressures were normal.

Decreased cardiac output was then documented in one patient by echocardiogram and in another by cardiac catheterization. In the first case, that of a 61-year-old man with atherosclerotic coronary artery disease, echocardiography was performed "because of the strong clinical impression that this patient's heart disease was not severe enough to cause the liver disease," Dr. Cohen said. The patient had been admitted with a six-week history of anorexia, fatigue and a 12-pound weight loss. But he was not hypotensive and had no signs of congestive failure, Dr. Cohen stressed. Echocardiography, however, revealed "poor myocardial contractility and a very low systolic ejection fraction of 15%."

In the second patient, a woman with rheumatic heart disease, cardiac catheterization for evaluation of increasing exertional dyspnea had been delayed because of unexplained high transaminase levels. When the procedure was ultimately performed it revealed a normal right atrial pressure, a "strikingly low cardiac index of 1.4 and critical mitral stenosis." After mitral valve replacement, the transaminase levels rapidly returned to normal.

In all patients, Dr. Cohen noted, successful treatment of the underlying heart disease led to improved or normal liver function tests.

"Pericentral necrosis has been described in hypotension, shock and low cardiac output states associated with myocardial infarction," Dr. Cohen concluded. "It probably results from hypoxic damage. We are now reporting an identical lesion presenting clinically as hepatitis. This lesion is presumably due to clinically unrecognized low cardiac output states in these five patients without hypotension or right-sided congestive heart failure and is potentially reversible." Coauthor was Dr. M. M. Kaplan.

Pulmonary Lavage Method May Replace Lung Biopsy

Medical Tribune Report

NEW ORLEANS—Bronchofiberscopic subsegmental pulmonary lavage is a safe and accurate means of evaluating immunosuppressed patients suspected of having pneumocystis pneumonia—the most common cause of diffuse pulmonary infiltrates in such patients—and may preclude the need for open lung biopsy, Dr. Jason Kelley, a Pulmonary Fellow at the University of Vermont, told the American Thoracic Association.

Other low morbidity diagnostic methods, such as bronchial brushing, percutaneous needle biopsy or aspiration, and endobronchial forceps biopsy have yielded a "significant number of false negative results," Dr. Kelley said. When findings are negative in the face of a strong diagnostic presumption, physicians have had to weigh whether to expose immunosuppressed patients, who are frequently physiologically unstable, to the anesthetic and surgical risks of open lung biopsy or institute empiric drug therapy, he stated.

Since pulmonary lavage specifically samples the alveolar space, where pneumocystis disease occurs, the technique was employed, following initial animal studies, on a trial basis in 15 patients in whom progressive pneumonia and fever suggested pneumocystis or other opportunistic pathogens. Three proved to have pneumocystis by lavage, and 12 showing negative results had either leukemic infiltrates, bacterial pneumonia, viral pneumonia, connective tissue disease or chemotherapy-induced fibrosis, confirmed by tissue diagnosis, bronchoscopic culture or response to altered chemotherapy.

"We were not compelled to perform open lung biopsy in any case," Dr. Kelley reported, and no patient with a negative lavage received pentamidine, the current drug of choice for treating pneumocystis infection. The drug may produce hypoglycemia, renal failure or pain at the site of injection, Dr. John Landis, principal investigator and Associate Director of Medical Services, the Medical Center of Western Massachusetts, noted in an interview.

The sole patient with a negative lavage who died did not have evidence of pneumocystis at autopsy.

Procedure 'Very Safe'

Later employed in over 100 patients and normal volunteers, bronchofiberscopic pulmonary lavage proved to be a "very safe procedure," Dr. Kelley continued. The two major risk factors encountered were hypoxemia and thrombocytopenia, but neither were considered contraindications. Seven hypoxic patients received supplemental oxygen during the procedure. In five thrombocytopenic patients, no bleeding episodes occurred during bronchoscopy. Two patients receiving ventilatory support via nasotracheal tube prior to bronchoscopy and 100% oxygen during the procedure died of bacterial superinfection unrelated to respiratory support at least seven days after pulmonary lavage.

New Camera Enables Bedside Nuclear Scan

Medical Tribune Report

DALLAS—A newly developed portable nuclear scanning camera allows radioisotope procedures to be brought to the bedside of critically ill patients, Dr. John A. Burdine, Professor of Nuclear Medicine, Baylor College of Medicine in Houston, reported here. The new Low Energy Mobile (LEM) camera was unveiled during the Society of Nuclear Medicine's annual meeting.

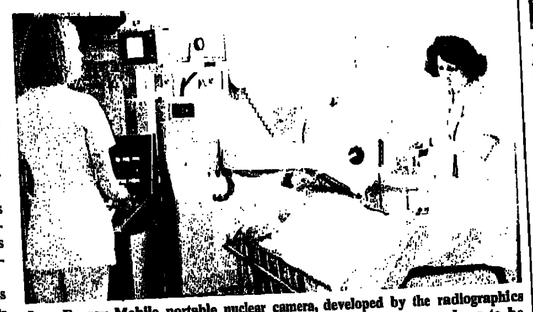
Dr. Burdine conducted clinical trials with the LEM over a four-month period involving 150 patients in St. Luke's Episcopal and Texas Children's Hospitals in Houston.

He found that the camera increases diagnostic capabilities without compromising patient safety and comfort. He predicted that the unit will probably receive wide accepance in cardiology, pediatrics, and orthopedics, where movement of the patient may be undesirable.

"While the usefulness of nuclear imaging procedures in the care of the critically ill is well understood, many of these patients are confined to circumstances where they cannot be transported to the nuclear medicine laboratory," Dr. Burdine said.

"With LEM, virtually all routine nuclear imaging procedures utilizing low energy radiopharmaceuticals may be performed at the patient's bedside."

The LEM camera, made by the radiographics division of G.D. Searle & Co., weighs 790 lbs., has a 250 kilo electron volt energy limit, and can do 80% of a standard camera's work.



Low Energy Mobile portable nuclear camera, developed by the radiographics division of G.D. Searle & Co., allows all routine radioisotope procedures to be performed at bedside, reducing patient movement and discomfort to a minimum.

Effect of Irradiation in Cancer: An Issue at Radium Society

Medical Tribune World Service

VANCOUVER, B.C.—The controversy regarding the clinical and prognostic significance of immunosuppression in irradiated cancer patients received wide attention here at the Fifty-Eighth Annual Meeting of the American Radium Society.

Does radiation therapy itself cause significant suppression of cell-mediated immunity? Yes and no, implied Dr. Charles McKhann, Professor of Surgery at the University of Minnesota. His studies of 150 melanoma and sarcoma patients show that they already had depressed immune responses, as measured both by T-cell rosette formation and by phytohemagglutinin (PHA) lymphocyte stimulation.

But this immunologic depression is intensified by current treatment modalities, Dr. McKhann said. Surgery, or possibly the anesthesia used with it, dampens cell-mediated immunity for a matter of days, and chemotherapy for weeks or months. Irradiation, he said, appears to dampen it for years.

Tests Too Sensitive?

Yet the clinical significance of such findings is not clear, Dr. McKhann pointed out. "We see T-cell depression in normal persons with a cold." Perhaps the T-cell rosette formation and PHA lymphocyte stimulation tests are "too sensitive." There are different subpopulations of T-cells, but it is not known which is protective. In any event, investigators "don't know exactly" what their findings mean.

The need for more definitive data was also cited by Dr. William M. Wara, Assistant Professor of Radiotherapy, Division of Radiation Oncology, University of California, San Francisco, who reviewed the pertinent scientific literature.

The "most controversial report" in the literature to date, Dr. Wara said, is that of Dr. Jan Stjernsward (*Lancet* I:1352, 1972), who attributed depressed cell-mediated immunity in breast cancer patients to irradiation of the thymus. This interpretation has "recently been challenged" by other investigators who have not only questioned "the statistical validity" and "follow-up time" of Dr. Stjernsward's studies, but also "demonstrated that inclusion of the thymus gland in the irradiated field was not a prerequisite for subsequent immuno-suppression."

Immunosuppression in irradiated patients has now been well documented, Dr. Wara said, but he agreed with Dr. McKhann that its significance "remains unclear." Accordingly, Dr. Wara raised two questions which he felt would serve to clarify the clinical issues in radiation therapy for neoplastic disease: "Is depressed T-cell immunity as evaluated in vitro related to patient prognosis and survival? And can this immunosuppression be altered by immunotherapy?

"Clearly," he concluded, "prospective controlled trials must be initiated to evaluate the effects of localized irradiation on lymphocyte subpopulations, as well as the effect of immunotherapy [BCG, transfer factor, levamisole, thymosin, etc.] on these patients. Only with these studies will we be able to determine the length and prognostic significance of immunosuppression caused by irradiation."

Partial Cystectomy Proves Useful in Some Bladder Ca

Medical Tribune Report

LAS VEGAS—Partial cystectomy may be equally as effective as total cystectomy in treating primary and secondary carcinoma of the bladder, a Cleveland Clinic team told a meeting of the American Urological Association.

Advocates of partial cystectomy cite as advantages: technical simplicity, diminished morbidity and mortality rates, and preservation of continence and potency. Proponents of radical surgery argue that partial cystectomy represents less than adequate treatment in terms of survival and ultimate cure rate, Dr. Andrew C. Novick explained.

Fifty patients underwent partial cystectomy as the primary means of treatment in the period from 1960 to 1972. The five-year survival rate was 67% for Stage O-A, 53% for Stage B, and 20% for Stages C and D1 combined, which compares "most favorably" with total cystectomy outcomes, according to Dr. Novick and Dr. Bruce H. Stewart, of the Department of Urology. Dr. Novick added that patients in whom free margins of resection were accomplished for unifocal disease achieved longer survival with less chance of developing recurrent bladder cancer.

12-Year Study

The 12-year study involved 43 males and seven females, with an average age of 64 years, who underwent partial cystectomy at the Cleveland Clinic and included all tumor types, Dr. Novick said. He added that during this period an additional 12 patients underwent partial cystectomy as adjunctive surgical treatment for primary gastrointestinal or gynecologic malignancies secondarily invading the bladder. Less favorable results were reported for this group of patients.

Patients with primary bladder carcinoma were considered for partial cystectomy under the following conditions: where tumors were confined to the bladder dome; tumors within a bladder diverticulum; solitary tumors overlying a ureteral orifice and/or involving the distal ureter; tumors not amenable to transurethral resection, and tumors in poor-risk patients.

Pediatric Practice

. . . presenting excerpts from current journal articles and commentaries of interest to physicians who treat children.

Splenectomy Risks?

"How can one reduce the risks [of infection] in patients with a valid indication for splenectomy? When possible, splenectomy in infants should be deferred. When it seems essential in children under five, it should be followed by phophylactic oral penicillin for at least three years. This practice might be extended to older children and adults with an immunological defect. Vaccination with polyvalent pneumococcal vaccine has been suggested but has not been submitted to trial. Subcutaneous implantation of splenic tissue prevents serious infection in splenectomised rats and has been suggested for application in man.[14] This would be inappropriate in Hodgkin's disease or chronic granulocytic leukaemia, and the number of patients in whom this technique might have a place is likely to be small. Where possible, damaged spleens should be repaired rather than removed. Unnecessary splenectomy incidental to intra-abdominal surgery in some large series is responsible for up to 30% of all splenectomies. In malarious zones, splenectomised patients should go onto malaria-suppressive drugs immediately and for life. The long-term hazards of splenectomy would be reduced if all concerned—doctors, patients, and patients' parents—became aware of the urgent need for treatment when infection arises." *(Editorial, The Lancet 1:1168, May 29, 1976)*

Correcting Immunodeficiency

". . . Owing to the laws governing the inheritance of the major histocompatibility antigens . . . a majority of infants [with severe combined immunodeficiency] will have no compatible potential donors [of bone marrow for transplantation]. The repeated dramatic reversal of the uniformly fatal prognosis in the disorder by grafts of compatible marrow cells over the past eight years has prompted the intensive search for alternative forms of definitive therapy when no histocompatible donors exist; with few exceptions, these efforts have been unsuccessful. In [our studies of] two unrelated male infants . . . fresh, very young fetal liver cells were used in attempted immunologic correction of the adenosine deaminase positive form of severe combined immunodeficiency. The observation of transient graft-versus-host disease in both infants documents the graft-versus-host potential of even this very young fetal tissue. More importantly, the successful immunologic reversal of the immunodeficiency in one of the infants confirms the usefulness of fetal liver cells as an alternative form of definitive therapy when bone-marrow transplantation cannot be performed." *(Rebecca H. Buckley, et al, New Engl. J. Med. 294:1076, May 13, 1976)*

One Man . . . and Medicine

ARTHUR M. SACKLER, M.D.
International Publisher, Medical Tribune

China: Trees and Art, Technology and Ecology

I HAVE COMMENTED on Allan Chase's observations on the medical ecologic bicentennial of Sir Percivall Pott's observation on coal soot, the cause of scrotal cancer in chimney sweeps. Our discussion ranged much wider. We agreed on the fallacies and dangers of neo-Malthusian doctrines; we wondered at the marvel of our industrial nation producing enough food both for ourselves and for scores of millions around the world with just 4% of our own population. Our discussion turned to the ability of the People's Republic of China to feed almost a quarter of the world's population, about three-quarters of a billion souls, sans our technology or mechanization.

I have long been interested in the archaeology and art of China and fascinated with their discoveries preceding those of the West in technology and in aesthetics. One has to see, to fully enjoy and believe, the solutions that Chinese painters achieved several hundred years before Cezanne, the Impressionists and even the Expressionists. Knowing of my interests, Allan couldn't resist telling me about a recent experience of his own.

Recurrent Theme

His sister and her husband had just returned from China. As he had suggested to them, they recorded the events of the day each evening. Allan had the opportunity of listening to the tapes in a few sittings. He noted a recurrent theme—again and again reference to the planting of trees, to the dispersion of factories, plants of small size sited in relation to an agricultural commune. It appeared that in contrast to the West which introduced the technology of the Industrial Revolution, there may be a difference in approach to mass production in today's China. Even as large-scale facilities are being built, as for manufacture of steel or generation of hydroelectric power, the Chinese appear to be significantly decentralizing and fostering small-scale manufacturing enterprises. The implications inherent in massive reforestation and in industrial decentralization raise many fascinating conjectures.

Admiration of Nature

With respect to reforestation, there has been extensive mobilization of the population ever since the Chinese communist revolution. The floods of China have constituted an historic tragedy with recurring devastation and disruption, disease and death. But can it not be that the reforestation of China is much more than just flood control? Have the Chinese leaders, consciously or unconsciously, mobilized men, women and children to the task of harnessing solar energy through the medium of chlorophyl and storing it in their forests?

I have long been sensitive to the Chinese admiration of nature, to their fascination with landscape. Their pictorial presentations relating to the physical and aesthetic qualities of bamboo had brought much of their painting close to my heart and awakened a passionate love of the aesthetic of Chinese calligraphy.

The Chinese philosophy, the way of thinking implicit in Chinese art, Chinese absorption with the multifaceted aspects of nature as reflected in the interweaving of multiple forms and themes into their iconography, may carry over in some measure to their approach to science and technology. Their art and poetry would quickly reveal the very pointed pleasure they derive from actions with a complex of significances. This may be true also for reforestation with its aesthetic effects on the landscape, its practical application as in flood control, its other pragmatic advantages in the creation and storage of natural resources and, come to think of it, even its biochemical benefits in ecologic terms—the conversion of carbon dioxide into oxygen.

Balanced Biosphere

The concept of life cycle and that of a balanced biosphere goes back millennia in China. It well reflects their realism and their empiric solutions which have contributed so much to the Chinese understanding and positive use of nature. Han ceramics recorded social customs at the time of Christ and one of them shows a privy perched on a pig-pen wall. There it was—a "balanced sty" rather than a "balanced aquarium." The pig ate "night soil" and the pig in turn was eaten. Night soil was also used to fertilize the fields whose bean sprouts and vegetables were so important a part of the Chinese diet. The cycle of food reflected a cycle of life.

Allan pointed out in relation to the dispersion of factories another interesting gain—the dilution of potential pollutants. As in so much of Chinese custom and action, we must go beyond a simplistic unitary motivation and even beyond the potential military implications; placing small factories in relation to agricultural communities is both time- and material-saving. Commuting to work, so much a part of the urbanized, industrialized western societies, is reduced if not eliminated. The physical state of the worker is improved by walking or pedaling a bicycle rather than by the application of the gas pedal of a car. Decentralization contributes more than a saving of time and the benefits of physical exercise. It reduces the waste of metals and fuel consumed and toxic pollutants produced by cars, buses and trains.

True Progress of Man

We can't avoid making comparisons and we must stress the danger of unidimensional thinking. It is high time we stopped looking at the problems of the world solely in terms of population numbers. With one-quarter of the population of China, our industrial plant can produce multiples of the environmental pollutants they do. Worse than that, we have replaced the biological benefits of man's excretia with the non-biodegradable and highly toxic "excretia" of an industrial society which can poison not only its soil and water but its people as well. Nature is remarkable—if we do not tortuously distort its cycle, as we unnecessarily do by unthinking industrialization. An automobile created by man pollutes. The natural by-products of man qua man, properly used, enriches. It cannot be that the Chinese will stand alone in recognizing that nature affords us a closed system in which man can physically as well as intellectually and spiritually live well, even as he enriches his world. There is nothing in our philosophy and there is much in our history which says that we, too, can meet the challenge and assure that industrial and technologic progress is tied, in more of its aspects, to the true progress of man.

Medicine on Stamps

Oliver Wolcott

Oliver Wolcott (1726-1797) was born in Windsor, Conn. Shortly after graduating from Yale, he was commissioned in the militia and served in the "King George's War." He then studied medicine as an apprentice to his brother. His medical career was rather limited, since he served as Army Surgeon only during the campaign against Burgoyne in 1775. He remained in public service for the rest of his life. In 1776 he was elected to the Continental Congress and is pictured in the above stamp as one of the signers of the Declaration of Independence. He is the 41st member from the left. He was elected Governor of Conn. in 1796 and served until his death. The nation's Bicentennial coincides with the 250th anniversity of his birth.

Text: Dr. Joseph Kler
Stamp: Minkus Publications, Inc., New York

EDITORIAL CAPSULES

. . . brief summaries of editorials or comments in current medical and scientific journals.

Need for Holistic Medicine

"The inability of physicians, psychiatrists included, to practice a genuinely holistic medicine that integrates knowledge of the body, the mind, and the environment is striking. Psychiatrists, for example, tend to adhere to one or another of the various ideologies in their field and to ignore the others; in spite of advances in neurochemistry and genetics, these disciplines often get little attention from psychiatric practitioners or training programs. Nonpsychiatrist physicians mainly interested in disease or dysfunction of a particular organ-system ignore the unaffected systems and the psyche.

"These attitudes persist despite pages of polemics about the importance of treating the whole person, and despite overwhelming evidence that a comprehensive understanding of man requires a general systems approach. . .

"Medicine must be an adaptive system of learning. Just as we expect people to be mature and effectively coping individuals, we must have the courage and the determination to study the forces that produce and maintain health and well-being, not merely the forces that produce disease.

"A failure to explore and counter the forces that sustain these dualistic splits will permit them to retard the development of a general systems approach by discouraging the transfer of information from neurophysiology to psychoanalysis, from small group and family dynamics experience to general practice, from neurochemistry to clinical psychiatry, from the social and behavioral sciences to general medicine, and so on and on. Pertinent knowledge will remain in the hands of the researchers and the universities and have virtually no impact at all on the physician and his practice. Under these conditions, medicine will see still further lowering of its status in the public eye. Our dissatisfied or unsatisfied clientele will search elsewhere, leaving us open to the charge that we are more interested in protecting our traditions than helping our patients.

"Breaking the grip of these dualities will permit medicine to recapture the whole person as the focus of attention and reduce those dehumanizing preoccupations with the disease alone, the psyche alone, the liver or the pancreas alone, the psychosis alone. This *is* holistic medicine for a society that needs to learn from the medical profession how to be an effectively caring society." *(Editorial, Roy W. Menninger, M.D., Ann. Int. Med. 84:604, May, 1976)*

EPIGRAMS—Clinical and Otherwise

Nor know that what disturbs our
blood
Is but its longing for the tomb.
William Butler Yeats
(1865-1939)
The Wheel

Harvard Community Brewing 'Genetic Engineering' Storm

Continued from page 3

"It's a cooling off period so that the council can hear evidence in a non-crisis situation," Mr. Pat Centanni, assistant to the Mayor, told MEDICAL TRIBUNE. "After that, we'll see."

The Harvard situation promises not to be an isolated incident but an augury of the future. A resolution before the Energy and Environment Committee of the U.S. Conference of Mayors proposes that investigators planning to perform any recombinant DNA research first notify the mayor and the legislative body of the community of their intentions. The resolution's sponsor? Mayor Alfred E. Vellucci, of Cambridge.

The public and political furor which threatens to engulf recombinant research distresses many scientists. They point out that all investigations have attendant risks. The impact of recombinant technology on society was a focal point of a recent Miles Laboratory-sponsored symposium held at MIT. MEDICAL TRIBUNE spoke with some of the participants.

No 'Fail-Safe' Research

"Recombinant DNA is a subset of a larger category of work," said geneticist Seymour Lederberg, Ph.D., of Brown University, Providence, R.I. "We've been working with animal DNA and viral DNA for roughly a generation. And in many cases recombinant DNA is safer to work with.

"Much of the time, we're working with a fraction of the viral genome and deliberately so. The overall impact of recombinant research may in many cases be to reduce risks," he told MEDICAL TRIBUNE.

"Take the example of producing vaccines against viral illness. We now have a crash program to produce a vaccine against swine influenza. To make the vaccine, large volumes of the virus must first be manufactured.

"If we had the gene for the protein coat of influenza virus—that's the only thing we actually need to produce the vaccine, it could be incorporated into E. coli. The bacterial cell would then make the influenza protein we're interested in. It wouldn't make the virus itself," he explained.

"I don't mean to minimize the hazards of DNA research. There's no such thing as fail-safe research. Despite the safeguards and the guidelines which have been set up, I'm assuming there will be human mistakes. It's plausible," he continued.

"But there's a trade-off. If we're so concerned about possible dangers, we might seriously consider expunging hospitals from cities. After all, they're a focal point of contagious and dangerous illness. But that's not very realistic, is it?"

Some critics argue that the information resulting from recombinant experiments could be obtained other ways.

"Well, yes and no," said Roy Curtiss, III, Ph.D., of the University of Alabama, Birmingham. "In some areas, for example in purifying eukaryotic genes, we don't have another way of extracting the information. In other areas, it's a judgmental opinion. Another technique might take longer, involve greater expense and give potentially less resolution.

'Accelerated Knowledge'

"In my own field, recombinant technology has accelerated our knowledge of replication of information in microorganisms. Certainly it could have been obtained by other methods. But with recombinant research we've learned three to four years worth of information about E. coli in only one year," he explained.

"It's going to be up to the investigator to make a decision whether recombinant DNA is the best approach," said Stanley Falkow, Ph.D., of the University of Washington in Seattle. "And despite all the indications we have, very likely this research will not be particularly hazardous."

Dr. Falkow believes that the "biggest biohazard is likely to be ignorance" of good laboratory technique among the investigators and their staff. Dr. Curtiss agrees.

"The probability of a catastrophic occurrence is minuscule where one uses a disarmed host-vector system, that is, a strain of bacteria which has been so weakened that it cannot survive outside of laboratory conditions," Dr. Curtiss told MEDICAL TRIBUNE. (He has developed two such strains of E. coli, labeled 1776 and 1876 in honor of the nation's bicentennial. "We're working on 1976," he said.) "Of course, the probability figures in no way factor in human error, ranging from sloppy technique to mistakes in judgment."

"There is a tendency for people doing this research to be molecular biologists and biochemists without a great deal of training in microbiology or microbiological techniques," Dr. Falkow notes. "It's surprising how much basic microbiology they don't know," echoes Dr. Curtiss. "We've had dealings with a lot of labs wanting to use our strains. But they can't get the bug to grow or transform."

As a remedy, basic courses in microbiological technique are being conducted at the University of Minnesota, Cold Spring Harbor, and at NIH facilities, according to Dr. Falkow.

Talk of 'Monsters'

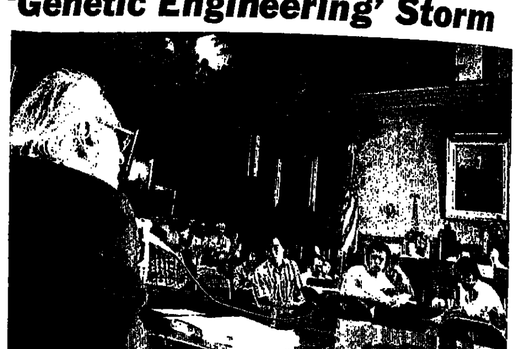
Dr. Lederberg, for one, however, believes that the press, with its talk of "monsters" escaping from the laboratory, has oversold the dangers of recombinant DNA research to the public. "The most notorious aspect of a story becomes the most glamourous," he says, a thought seconded by Dr. Stanley Cohen, of Stanford University.

"The news media with its emphasis on all or nothing research is laboring under a misconception," Dr. Cohen told MEDICAL TRIBUNE. "Everyone agrees that certain experiments should not be carried out. But I don't know one responsible scientist who wants to see this research halted."

Dr. Cohen is quick to point out that it was the researchers themselves who research and in a fairly drastic, although not unprecedented move, declared a voluntary moratorium on some experiments while guidelines for future investigations were promulgated. The now legendary Asilomar Conference in February, 1975, classified experiments according to risk (banning some for the present), set laboratory standards for each category, and indicated appropriate host-vector systems to be used.

Revised and expanded, these recommendations form the basis of the NIH guidelines on recombinant DNA research issued at the end of June. Scientists expect that the guidelines, which apply only to NIH-funded research, will also be accepted by private laboratories here and investigators abroad.

However, the controversy may not be over technical safety so much as ethical considerations, suggested Dr. Curtiss, a view shared by Dr. Roland F. Beers, Jr., of Miles Laboratories.



Dr. George Wald, Nobel prize winner (1967) in physiology and medicine and Higgins Professor of Biology at Harvard, testifies at public hearing of Cambridge, Mass., City Council, held to consider granting Harvard permission to build a high-security lab where recombinant DNA research would be carried out.

"The proponents of moratoriums on research for the purpose of restricting knowledge about man and his universe and the direct attacks on technological change are to be recognized as human responses to the fear of the unknown, but implicit in this response is a distrust of the human intellect to perform adequately toward the threatened risks," Dr. Beers told the symposium.

"I think the ultimate concern of many critics is the genetic manipulation of human beings," Dr. Curtiss told MEDICAL TRIBUNE. "The general philosophy seems to be that in order to avoid the last step you have to preclude the first one. But we'll have the opportunity to make assessments all the way along the line. I'm an optimist —by taking the first step, you don't predetermine you'll take the last."

Coronary Artery Aneurysm: Less Rare Than Suspected?

Medical Tribune Report

PHILADELPHIA—Eleven new cases of coronary artery aneurysms, bringing to 34 the world's known total of this disorder, were reported here by a University of Iowa team.

Suggesting that the condition may be more common than is now suspected, Dr. Herman L. Falsetti said the Iowa series was identified in a population of 742 patients who were referred for cardiac catheterization and coronary arteriography from July, 1973 to April, 1975.

The prospective study showed the clinical picture in patients with coronary aneurysms to be similar to that of severe coronary artery disease, diagnosis being possible only by coronary arteriography, Dr. Falsetti told the American College of Physicians.

The 11 patients in the series, including 10 men and one woman, ranged in age from 35 through 69 and had had symptoms from one month to 14 years. Five patients had had previous myocardial infarctions.

In 10 of the 11 patients, the coronary artery aneurysms were multiple and associated with extensive coronary atherosclerosis. Left ventricular function was impaired when measured by end-diastolic pressure, end-diastolic volume and ejection fraction, the investigator said. Segmental left ventricular pressure contractions were "severely abnormal."

"There is no significant difference in the distribution of aneurysms between those thought to be atherosclerotic or those due to congenital or other malformations," he observed. "In general those due to trauma or mycotic in nature are often single. Those secondary to inflammatory disease, such as polyarteritis or atherosclerosis, are multiple. To be emphasized, however, is that the presence of one coronary artery aneurysm should lead to the suspicion of others in the heart as well as other parts of the body."

Seven patients in the Iowa series and eight in the published reports underwent surgery, Dr. Falsetti noted. Thirteen were alive in the immediate postoperative period, and of our seven patients all are still alive and have had improvement in their symptoms." Dr. Falsetti is Professor of Medicine at the University of Iowa.

Interview Probes Decision to Immunize All

Continued from page 1

other medications, and the usefulness of other available agents, such as antibiotics and amantadine, in curtailing the ravages of an epidemic.

In discussing the reasoning behind the planned utilization of 200 million doses of the monovalent vaccine and 20 million doses of combined swine and Victoria vaccines for high-risk persons, Dr. Cooper told Dr. Sackler that "the entire population is susceptible to infection."

Stockpiling Discarded

And because a flu epidemic "can spread like fire," the HEW Assistant Secretary for Health said the stockpiling option was discarded. Too much time would elapse between a given outbreak and activation of a vaccination program, he stressed.

Asked why, then, the government could not move as quickly in clearing drugs against such other problems as cardiovascular disease and high blood pressure, Dr. Cooper cited "differences between biologicals and other forms of pharmaceuticals."

Dr. Cooper specified, for example, that "the information we have regarding toxicity and effectiveness of other influenza vaccines developed and used in recent years is generally applicable to this vaccine." Furthermore, he said, "the swine flu threat is considered imminent, and there is no other way to prevent the potential morbidity and mortality. . . ." On the other hand, noted Dr. Cooper, cardiovascular drug treatments "are already available covering such drug class and each disease factor. The basis of approval for each type of therapeutic agent must rest on sound scientific principles and substantial evidence of safety and effectiveness . . . as required by the Food, Drug and Cosmetic Act."

The HEW official conceded that "although prevention is the only way to curb high morbidity and mortality from influenza . . . antibiotic therapy [is] very important." Antibiotics "will almost certainly be employed," he said, though in some cases this therapy may be "too late" or "insufficient."

Considering the hypothetical protection against viruses offered by massive doses of ascorbic acid, the availability of amantadine—a drug with antiviral effects, and the unpredictability concerning an epidemic, wouldn't it be as logical, Dr. Sackler asked, to support such measures as to support the program?

"The value of massive doses of vitamins still remains to be established [and] expert opinion still does not consider amantadine a replacement for the vaccine," replied Dr. Cooper.

In the next issue: Dr. Cooper discusses the results of clinical trials with the swine-type vaccine, the possible need for a damage compensation mechanism, and the reliance on "past experience" for chronic toxicity data.

The first injection of experimental swine flu vaccine went into Dr. Harry Meyer, Director of FDA's Bureau of Biologics. Preparing to give the shot is HEW's Assistant Secretary for Health, Dr. Theodore Cooper.

Dr. Comfort Urges Caution in Prescribing Drugs for Elderly

Medical Tribune Report

LOS ANGELES—Drugs can and do play a key role in helping the older man or woman cope with the fears, anxieties, depressions and psychoses that accompany advancing age, Dr. Alex Comfort told a meeting of the American Geriatrics Society here. However, the geronological expert warned, the physician must be sure that the elderly patient's emotional and psychiatric disturbances have not been brought on or exacerbated by overmedication.

"The prescription of any drug, even aspirin, is no light matter," Dr. Comfort said. "Old people go crazy because they were crazy when they were young, because they are ill, or because we drive them crazy. Many older patients are overmedicated with drugs they have bought themselves over the counter or which have been prescribed by doctors. In many cases, old people are just simply zonked out."

Plastic Bag Therapy

When treating an elderly patient, the physician's most important tool may be a plastic bag, Dr. Comfort counseled. "The bag should be given to the patient or to his family to collect all the medications the patient is taking. Sometimes a very large bag is necessary because the patient may be taking as many as 20 or 30 different medications."

Once the patient has been weaned of his vast supply of drugs, a proper assault on the patient's problems may begin. According to Dr. Comfort, successful control of psychiatric and emotional disturbances can be achieved with treatment that includes counseling, occupational and recreational activities—and a well-controlled drug regimen.

Depression, for example, will respond to any of several drugs, including tricyclics, methylphenidate, phenelzine, and tranylcypromine, Dr. Comfort said. "Methylphenidate should be used in small amounts or you'll send your patient up the wall. Phenelzine could be used for depressions marked by obsessions and tranylcypromine might be worth trying before ECT."

ECT, Dr. Comfort said, if cautiously but adequately used, could be useful against depressions, especially those marked by suicide threats. "And," Dr. Comfort added, "Don't be afraid to talk to the patient about suicide. You won't cause it . . . And you may prevent it."

The elderly hypochondriac will also respond to proper treatment. "The last thing the hypochondriac needs," Dr. Comfort cautioned, "is a detailed explanation that his disease is psychosomatic."

Moreover, the hypochondriac should not be subjected to a series of needless surgeries meant to placate or, worse, to punish. "Don't approach with the philosophy that 'if the old bat thinks she has cancer then, by God, let's do a bronchoscopy and show her,'" Dr. Comfort said.

Proper treatment for the hypochondriac includes adequate observation, a prescription for an inert, mildly unpleasant placebo, and a follow-up appointment in two or three weeks.

To treat paranoia adequately, Dr. Comfort said, the physician must learn to distinguish between the real thing and well-founded anger. "Old people," Dr. Comfort said, "do have a tough road in our culture and not every complaint is paranoia."

One hint: "In most cases, the paranoia relates to domestic matters. It's not that the Nazis are out to get him, but that someone is stealing the mail—meaning that they forgot to mail letters or to write—or that people are always throwing dirt into the laundry—meaning that they forgot to turn on the washing machine."

Once paranoia has been adequately diagnosed, Dr. Comfort said, a major tranquilizer, administered in low dosages and in liquid form, may very well alleviate feelings of persecution and discrimination. "But be sure to give the tranquilizer in a liquid form," Dr. Comfort emphasized. "Paranoids have a thing about pills. They think people try to poison them with pills and will usually just hide them behind their dentures and spit them out later."

Ventilating Anxieties

The acute and chronic anxieties that are brought on by moves or other changes in the environment respond well to simple crisis intervention. "Help the patient ventilate his or her anxieties," Dr. Comfort suggested. "Help them relearn the environment."

Because older people worry about changes in their sleeping patterns, they should also be taught that with advancing age, sleep requirements and sleep habits change. "In old age, stage three sleep is short and sleep, generally, is lighter," Dr. Comfort said. "Reassure the patient that the new sleeping patterns, including daytime catnaps, are normal. Milk-based hot drinks are effective in helping the patient sleep."

Sleeplessness brought on by agitated depression, mania, or by acute anxieties, Dr. Comfort added, can be treated for two or three days with tricyclics, a major sedative or a nonbarbiturate hypnotic.

When the patient is burdened by so-called nursing home disease—a disturbance marked by blunting, regression, depression, and pseudodementia—therapy is often effective. Because the syndrome is triggered when the patient loses his job, is abandoned by his family or is treated as incompetent, Dr. Comfort said, it can be alleviated by giving the patient an adequate personal and social environment. "The patient can and does recover if real social responsibilities are imposed," Dr. Comfort said. "But the patient should not be oversupported."

Often, Dr. Comfort said, nursing home disease is mistaken for chronic brain syndrome. True chronic brain syndrome can be diagnosed by—among other things—testing the patient's ability to carry out sequential tasks. Chronic brain syndrome, Dr. Comfort said, can be reversed with drugs. But the best treatment, he added, may be the treatment which, given earlier in life, prevents the onset of the syndrome. Effective treatment of hypertension may be one way of preventing the later appearance of the syndrome.

Elderly people, Dr. Comfort summarized, will respond to proper medical approach. But the doctor must avoid the "false assumption" that the aging process inescapably renders men and women nasty, asexual and incompetent.

"We must also avoid iatrogenic disease," Dr. Comfort emphasized. "Drugs should be used fearlessly if indicated. But they should not be prescribed in large numbers and they should be reviewed periodically."

Dr. Cooper Explains Rationale Behind Swine-Type Flu Shots

Continued from page 1

Was the one death at Fort Dix enough to trigger a national vaccination program?

I should like to stress that the judgment to go forward with a national immunization program was not based solely on the finding of one death at Fort Dix. The dominant reason was that a significantly different flu virus had shown up in an influenza outbreak and had been involved in person-to-person transmission of the disease.

Historically, whenever the influenza virus has undergone a major antigenic shift, and caused a limited outbreak, a major epidemic has followed. In this case, the swine virus has not been identified in person-to-person transmission of the disease for many years. Therefore, virtually the entire population is susceptible to infection.

There is developing debate as to whether the government overreacted. How sure are we that we are going to have an influenza epidemic this year?

I believe we had no choice as public officials but to take the action we did to protect the public health, even though we do not know for sure that there will actually be an epidemic of influenza this fall or winter caused by the swine-type virus now designated as A/New Jersey/76. The decision does show that the government can act with dispatch when it needs to protect health.

Didn't the government have the option of preparing the vaccine, stockpiling it and/or using it in high risk groups?

We considered this option early but discarded it; an influenza epidemic can spread like fire. It would take 10 to 13 weeks from the time we had notice of further swine influenza outbreaks to activate an immunization program, motivate the public to participate, and give the shots. Then it would take two or three additional weeks after vaccination for antibodies to build to an appropriate level. I seriously fear that we could never get ahead of an outbreak in this manner. Furthermore, there would be no saving in cost.

You point out that the "government can act with dispatch when it needs to protect health," but there seems to be no dispatch in government actions in relation to a wide range of drugs for the treatment of the largest "epidemic" cause of death in the U.S.—cardiovascular disease, including high blood pressure. How do you explain this?

I would caution you about comparing approval and use of a vaccine against swine flu, and FDA approval of drugs, for example against high blood pressure. These are three points here:

First, there are differences between biologicals and other forms of pharmaceuticals, and the requirements for information necessary to certify safety and effectiveness vary.

Second, this is not a new vaccine entirely. Other vaccines have been developed and used against other forms of influenza for the past 30 years. The only major difference between this one and the others is in the antigenic qualities of the virus itself. It is not as if we were developing a totally new agent here. The information we have regarding toxicity and effectiveness of other influenza vaccines developed and used in recent years is generally applicable to this vaccine against the swine-type virus.

Third, I agree with you that there is also an epidemic of cardiovascular disease to which high blood pressure is contributor. There are also drugs now available in this country which are effective in the control of hypertension, but there is no drug on the market for the practical treatment of influenza, and no specific preparation generally available—yet—for the prevention of the disease caused by the A/New Jersey/76 strain.

Government regulations for new drugs require proof of efficacy and safety even for minor variations in a particular drug class. The government does not approve a drug on the basis of an immunologic or bacteriologic theory or principle, as you indicated for the flu vaccine. Why would you not favor more vigorous action than we have had for almost 10 years in the clearance of new cardiovascular agents?

The fundamental differences between the current vaccine situation and the cardiovascular situation are these:

The swine flu threat is considered to be imminent, and there is no other way to prevent the potential morbidity and mortality except by the proposed measures. With respect to cardiovascular diseases, there are drug treatments already available covering each drug class and each disease factor requiring treatment. The basis of approval for each type of therapeutic agent must rest on sound scientific principles and substantial evidence of safety and effectiveness based upon adequate and well-controlled studies as required by the Food, Drug and Cosmetic Act.

Mere demonstration of a pharmacologic effect of a cardiovascular agent is insufficient to assure that the particular agent will be safe and effective in humans, although some predictions in this regard can be made in the case of minor molecular modifications of already existing drug entities. Even in these cases, however, adequate preclinical and clinical studies are needed to establish that the predictions are correct.

You have said prevention is the only way to curb high morbidity and mortality from influenza. Do we not also have other means such as improved nutritional status and, of outstanding significance, the availability of antibiotics that are effective against secondary bacterial infections which were a major source of mortality in the 1918-19 epidemic?

Although prevention is the only way to curb high morbidity and mortality from influenza, nutritional status and antibiotic therapy are very important. Antibiotics will most certainly be employed. However, certain strains of flu can cause complications quite rapidly. In such cases, especially in patients with cardiovascular and respiratory disease, antibiotic therapy may be too late or insufficient to prevent morbidity and mortality. The best and most established medical practice is to prevent flu in the first place and use antibiotics as needed.

Theoretically, nutritional status could have some overall affect on influenza disease. However, this would seem to be most important in populations where a high percentage of people were in poor nutritional states, such as populations of developing countries. Nutritional status would not be expected to have a major impact in the United States.

You indicated that there are no drugs on the market for the treatment of influenza but there are for cardiovascular disease. This raises two considerations:

1. Pauling has raised the theoretical point that massive doses of ascorbic acid may be of importance in respect to an epidemic of swine flu because of the effect of ascorbic acid, metal ions and oxygen on nucleic acids and proteins which he maintains "leads to inactivation of viruses and contributes to the control of viral diseases by Vitamin C."

2. Other physicians point to the availability of amantadine. Thus, a nutritional supplement may hypothetically afford some measure of protection over a wider range of viral organisms, in contradistinction to the high specificity of a vaccine. In the other instance, there exists the claim for antiviral effectiveness of a drug for treating an existing viral infection. Furthermore, unpredictability as to whether we will have an epidemic at all or what type it will be is widely acknowledged. Wouldn't it be as logical to support the expertise of such scientists as Pauling as to support the expertise of those who advocate the vaccine? There is debate in both arens. Should the government take a partisan position? If such a partisan position cannot be supported by hard data but by expertise, judgment and theoretical considerations, should not similar criteria be applicable in both instances?

In any position the government takes there is usually going to be a difference of opinion. But the data upon which expert opinion is based must be the best possible. The value of vaccines has already been repeatedly demonstrated. The value of massive doses of vitamins still remains to be established. The OTC Cough and Cold Panel and the OTC Vitamin and Mineral Panel did not find high doses of ascorbic acid to be effective in respiratory disease of viral origin.

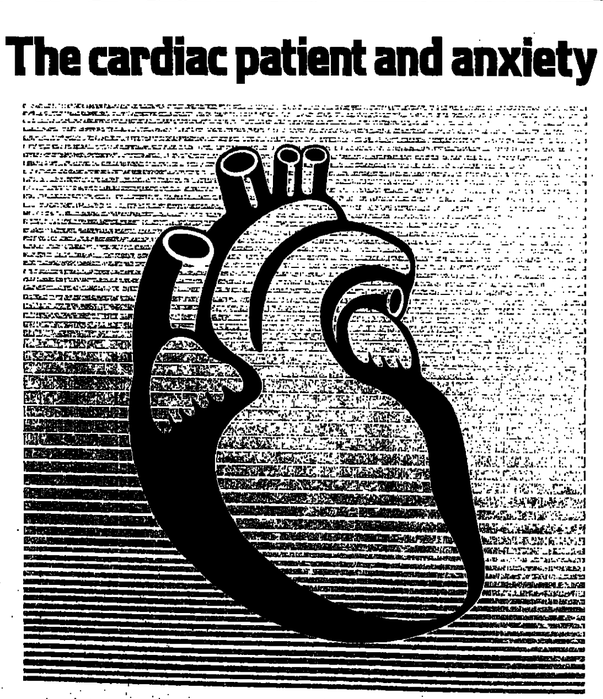
Amantadine is one agent that represents a new approach to treatment of viral illnesses. There is some evidence that amantadine can help in symptomatic improvement of infections due to influenza A strains but the mechanism of action is as yet undetermined. Expert medical opinion still does not consider amantadine to be a replacement for vaccine. For patients who cannot take the vaccine, amantadine may be an alternative second choice treatment. Thus, the path that the government has chosen to recommend is based on the best available medical evidence.

Continued Next Issue

On March 24, President Ford, flanked by Dr. Jonas Salk (left), Dr. Cooper, and Dr. Albert Sabin (right), announced on this page, Dr. Cooper points out the government's different approaches when bringing out a new form of vaccine crash immunization against swine-type flu. In interview text and approving an entirely new drug.

WHEN ANXIETY INTERFERES

The cardiac patient and anxiety



"The [cardiac] patient is anxious about minor symptoms, about the implications of his diagnosis, and about real or imagined limitations of function."*

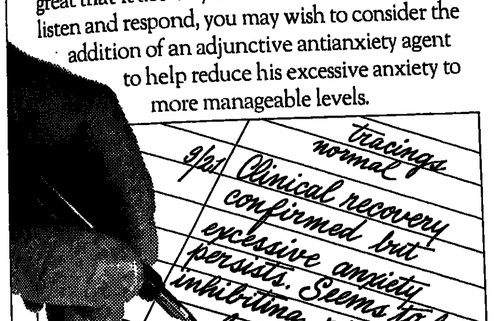
The worst is over. The cardiac patient is out of the acute stage, out of the hospital, and well on his way to recovery. How quickly he comes back to near normal functioning may depend on his psychological as well as his physical rehabilitation.

Clinical anxiety, for example, may be one reason for prolonged recuperation following cardiac healing. Yet anxiety can sometimes be beneficial in facilitating patient compliance.

The patient who is realistically concerned about resuming his precoronary functioning may be highly motivated to adhere to his rehabilitation regimen. However, the cardiac patient with *excessive* or unresolved anxiety may be so fearful of future heart failure that he refrains from your prescribed regimen.

Excessive anxiety can interfere with patient management

When excessive anxiety diminishes your patient's ability to participate fully in his rehabilitation program, your counseling and reassurance are often sufficient. But when his anxiety is so great that it actually interferes with his ability to listen and respond, you may wish to consider the addition of an adjunctive antianxiety agent to help reduce his excessive anxiety to more manageable levels.



Librium® (chlordiazepoxide HCl) an effective adjunct to your reassurance and counseling

Safety: Librium has a highly favorable benefits-to-risk ratio and a wide margin of safety. Because of its low incidence of side effects, it is regarded as one of the safest antianxiety agents available. And Librium does not adversely affect the cardiovascular system. See complete product information for warnings, precautions and adverse reactions.

Performance: Hundreds of clinical trials, thousands of published papers, and millions of patients constitute the record of performance for Librium.

Concomitant use: Of special significance in treating the cardiac patient already taking multiple agents is the fact that Librium is used concomitantly with most primary medications, such as cardiac glycosides, diuretics and antihypertensives.

*Zohman BL: *Geriatrics* 28:110-119, Feb 1973

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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Hip Joint Healing May Avoid Surgery

Continued from page 3

ics correlated with the patients improved clinical status.

All of the youngsters, the investigator stressed, had received intensive physical therapy as inpatients in a rehabilitation unit, and all were instructed to maintain a vigorous home exercise program after discharge. All were on a regimen of salicylates and indomethacin, in addition to other anti-arthritic drugs.

Illustrated Case

In a typical history, Dr. Bernstein cited the case of a 12-year-old girl with systemic JRA of nine years' duration, who had severe hip joint pain and needed two canes to walk short distances. Radiographs (see page 1) showed narrowing of the hip joint spaces and subchondral cysts of both acetabulae and femoral heads.

"Three years later she had no pain, was ambulating without assistance and was able to ride a bicycle," he noted. "Radiography demonstrated widening of joint spaces and sharp cortical margins of the acetabulae and femoral heads.

"In view of the children's improvement," he continued, "it seems unlikely that the increase in joint space was due to joint effusion. Rather, some new articular surface appears to have been provided for joints which previously were almost denuded of cartilage."

Dr. Bernstein observed that a variety of recent studies have challenged the concept that damage to cartilage is irreversible. He cited the widening of the hip joint that has occurred in some adults following successful femoral osteotomy for osteoarthritis of the hip. Further, he said, experimental studies have shown that the major components of joint cartilage can be renewed even in mature animals; and surgically created defects through cartilage into the subchondral bone may be followed by resurfacing of the joint with tissue having the histologic characteristics of cartilage.

Child's Potential Greater

"It appears possible that, because of a child's greater potential for growth and for remodeling of bone," he declared, "the likelihood of joint restoration is greater than in the adult."

The implications for therapy, his paper suggested, is that an aggressive rehabilitation program, stressing physical activity, combined with an appropriate medical regimen, offers the most promising chance of joint recovery. Dr. Bernstein commented that in the studies of animals with surgical defects, "new cartilage developed while the animals were permitted free movement; and the cartilage developed at a more rapid pace in the weight-bearing than in the nonweight-bearing areas of the joint. It is possible that a similar situation may have occurred in our patients."

In an interview, Dr. Bernstein's collaborator, Dr. Helen Kornreich, Associate Professor of Pediatrics, said the findings suggest that caution should be exercised before radical bone surgery is recommended in patients with JRA. The fact that joint function may be restored in some patients, suggests, she declared, that "we can't always predict the damage is irreversible." Coauthors included Dr. Deborah Forrester.

Acute Lymphocytic Leukemia Termed a 'Curable Disease'

Medical Tribune Report

WORCESTER, MASS.—Calling acute lymphocytic leukemia in children a "curable disease," Dr. Emil Frei, Director of the Sidney Farber Cancer Institute, Brookline, Mass., told a medical symposium here that if the child receives definitive treatment at a major center specializing in childhood leukemia and remains in complete remission with no relapse for five years, there is only roughly one chance in 10 that a relapse will occur in years five to 10. After 10 years disease free, the probability of relapse is almost nil, Dr. Frei added. Treatment continued longer than two years in these cases offers no advantage in avoiding relapse.

89% Disease Free

Speaking at St. Vincent's Hospital to a symposium on leukemia sponsored by the Leukemia Society of America, Inc., Central Massachusetts Chapter (Worcester), and the hospital, Dr. Frei, Professor of Medicine at Harvard Medical School, reported on 39 children treated at the Sidney Farber Cancer Institute who were taken off their drugs after two or three years of treatment. Thirty-five (89%) of the children are today completely free of disease.

Of four children in the original series (85 children), one died during the initial attempt to induce remission and three others died with a later revised diagnosis of undifferentiated leukemia. Dr. Frei stressed that these last three children had a different disease than the surviving children who had classic acute lymphocytic leukemia (ALL). He said that a review of a similar series from another major cancer center treating large numbers of children with acute leukemia corroborated the results at Sidney Farber. Of roughly 106 children in complete remission, only 10% had a relapse after they were put into remission.

Treatment of acute leukemia in children was "a major success story in cancer chemotherapy," Dr. Frei said. In children with classic ALL, he said, nine out of 10 are alive and disease-free at 36 months. Extrapolating from earlier series, the survival figure will be 80% at five years and will not be significantly lower at 10 years.

Dr. Frei urged the audience to encourage parents bringing children for treatment to think of the disease as a curable one, although he cautioned that he himself is careful never to tell a parent that his child can be cured, only that the disease is curable.

If the parents are not intimately involved in the treatment plan from the beginning, toxic side-effects of the drugs (falling hair, nausea, vomiting) will add unnecessary psychological burdens to the family, Dr. Frei said.

He said that treatment must be thorough, exact, and should be undertaken only at medical centers with the experience and resources to offer the best chance of successful remission.

Dr. Frei's explanation for successful cure in these cases was that acute lymphocytic leukemia in children, as in all diseases, follows the rule that relapse, if it comes at all, will generally come early in the disease.

The proof of this, he said, is that if treatment is administered early, complications from leukemic cells later invading the brain and spinal cord drop from a rate of 50% to 5% or 10%.

"X-ray treatment to the central nervous system should be factored out of treatment, if possible," he said, adding that various encephalopathies, not well understood, have appeared in some children treated with a combination of high-dose methotrexate and x-ray.

Very high doses of methotrexate without x-ray and followed by a "rescue" drug technique (citrovorum factor) are showing good preliminary results, he said.

Noting that a child at diagnosis carries 10^{12} leukemic cells in his body, Dr. Frei said it is not possible to eradicate the "one" remaining leukemic cell that may still exist after a successful course of chemotherapy. "This is not just looking for a needle in a haystack," he said, "it is looking for an atom in a haystack."

It is important to know, Dr. Frei added, that the percent of cells in the tumor load that are killed remains constant whether 10^{12} cells are killed with the first dose of drugs, or whether only 10^6 cells are killed. The same dose of drug is needed.

Because of the kinetics of cell division, as zero leukemic cell population is approached, none of the usual rules seem to hold, Dr. Frei said. Some other defense mechanism must then keep the reduced number of leukemic cells from producing any signs or symptoms of the disease in the child.

He suggested that the immune system probably takes hold and keeps the remaining cells in check, keeping the child in continuous remission and free from any clinical signs of leukemia.

The evidence that an abnormally functioning immune system is somehow involved in leukemia is that if the T lymphocytes of the patient (one of the two major classes of immune lymphocytes) fail to kill leukemic lymphocytes, the prognosis for the patient is poor. This depressed T-cell activity is the single most important indicator of a poor prognosis in the disease, he said.

Fewer Infections

Other poor signs, Dr. Frei said, are identification of the leukemic cell itself as a T-cell, the presence of a mediastinal mass, and a very high white cell count at diagnosis.

Intermittent courses of drug treatment lead to fewer infections than continuous dosing, and they give the blood-forming bone marrow and lymphoid tissues a chance to rest and produce a new population of normal cells, Dr. Frei said.

Dr. Frei cautioned that preliminary studies seem to show that the rate of appearance of second tumors later in life is linked to drugs that disrupt the DNA of the leukemic cells most directly, but not to the antimetabolite drugs, such as folic acid antagonists, that interfere with the protein synthesizing mechanisms of the cell.

Asbestos Workers Protest Job-Related Deaths

Protesting the reportedly asbestos-related deaths of 11 fellow workers in 18 months, employees of Johns-Manville Corp., Long Beach, Calif., picketed the plant. Workers want clause in contract to cover asbestos-related illness.

Tribune Economic Analysis

Utility Prices: Bellweather of Stock Trends

BY ELIOT JANEWAY
Consulting Economist

Any move in stock prices in which the utilities do not participate is suspect. A unique group, they are the only stocks that combine the characteristics of IBM and government bonds. They were growth stocks before the growth cult came into speculative vogue, and they have always been income stocks. Twenty years ago, every aggressive, professionally-managed portfolio started out with 25% of its assets invested in a cross section of utilities.

The tricky market history of 1976 has been delineated by the utility stocks. During the worst of the bear market, they seemed the least likely candidates for market leadership. Late last year, however, the utilities forged into the forefront as market performers.

The utility stocks ran out of steam last spring. The market realized that the recovery was not building a firm foundation of economic growth free from inflation. Again, the utilities were the bellwether of market performance. Once they stopped going up, the rest of the market started going down.

The realization that utility stocks had become overpriced relative to the cost of inflation prompted many utility stockholders to test the ability of the market to absorb selling. They quickly found that ability lacking, and buying of utilities stopped.

But the investment environment is gradually changing again, this time for the better. It reflects a practical recognition in the money markets that the bond market drop was overdone.

Investors who were alarmed by their inability to unload utility stocks last spring are suddenly eyeing them as attractive buys.

Ask Janeway

My son has an ocean front lot in Florida, and has proposed that I invest $40,000 in a house to be built on it. Do you consider this a wise investment and/or a tax shelter?
Cincinnati Physician

Your son's ocean front lot will be worth more if held with a view to taking money out of it in the future, than if you put money into it now. New homes are still more advantageous to buy than to build. No resort or second home is a tax shelter.

Send your questions on finances, investments, taxes to Janeway, MEDICAL TRIBUNE, 880 Third Avenue, New York, N.Y. 10022.

Simple Lab Tests Aid Diagnosis of Secondary High BP

Medical Tribune Report

DALLAS—A complete medical history, physical examination and simple laboratory testing can provide the physician with a 90% accurate detection of secondary hypertension, Dr. Norman Kaplan, of the American Heart Association, told a meeting here of the Society of Nuclear Medicine.

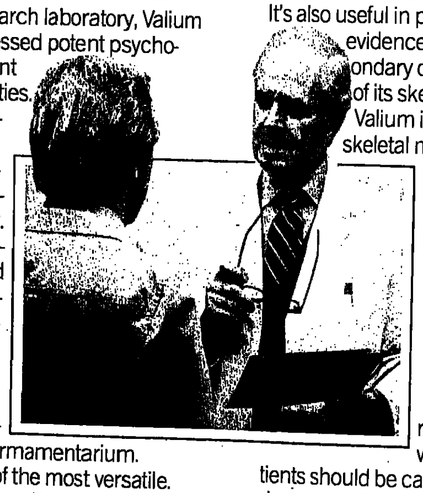
If the initial examination and tests suggest secondary hypertension, additional testing may be required, said Dr. Kaplan. If, for example, the patient is suspected of having:

- Chronic renal disease, additional tests may include BUN, creatinine and intravenous pyelogram (IVP). If positive, renin assay or renal biopsy.
- Renovascular disease, tests include IVP and plasma renin. If positive, renal vein renin and an aortogram.
- Coarctation, blood pressure in legs may be taken, followed by aortogram.
- Primary aldosteronism, testing may include plasma potassium, urinary potassium, plasma renin, plasma or urinary aldosterone.
- Cushing's syndrome, testing includes plasma 17-OHCS after 1 mg dexamethasone, and urinary 17-OHCS after 0.5 and 2.0 mg dexamethasone every six hours for two days each.
- Pheochromocytoma, tests may include a spot urine for metanephrine, urinary norepinephrine and epinephrine.

"No patient will need all of these procedures and relatively few will require any of them," Dr. Kaplan said. However, since idiopathic hypertension is incurable, attempts should be made to identify reversible forms.

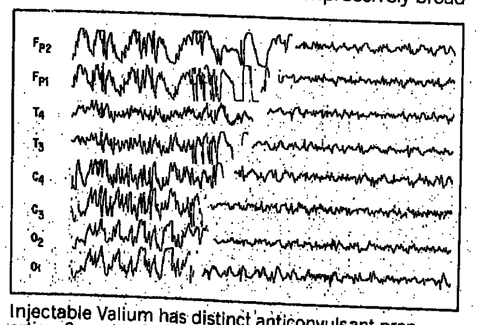
Valium® (diazepam) differs from other benzodiazepines

Valium (diazepam) is the one benzodiazepine with three clinically useful pharmacologic properties In the research laboratory, Valium demonstrated that it possessed potent psychotherapeutic, muscle relaxant and anticonvulsant properties. But the crucial question remained: would these three properties prove to be clinically useful? Extensive clinical testing gave the answer. Yes. Of all the available benzodiazepines, Valium – and only Valium – has three valuable pharmacologic properties that have *all* proven to have definite clinical utility. Clearly, this makes Valium one of the most useful agents in a physician's armamentarium.

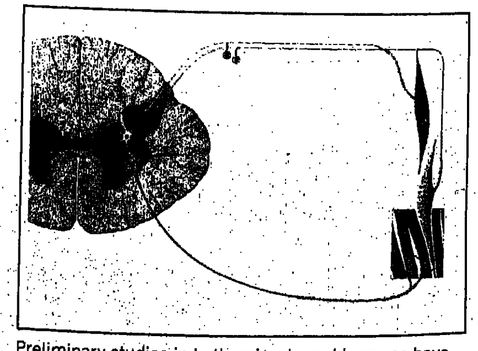


And, quite likely, one of the most versatile. Today, Valium is indicated in an impressively broad range of disorders. As a psychotherapeutic agent, for instance, it's useful for the relief of undue psychic tension and anxiety whether seen alone or associated with organic and functional disorders. It's also useful in psychoneurotic conditions evidenced by anxiety with or without secondary depressive symptoms. Because of its skeletal muscle relaxant effect, Valium is a valuable adjunct in relieving skeletal muscle spasm caused by strains, sprains or inflamed skeletal muscles. And its potent anticonvulsant action makes it a preferred drug (given adjunctively I.V.) in status epilepticus.

Drowsiness, ataxia and fatigue are possible side effects, but these and more serious adverse reactions are rarely a problem. Of course, as with all CNS-acting agents, patients should be cautioned about driving, operating dangerous machines or the simultaneous ingestion of alcohol while taking Valium (diazepam).



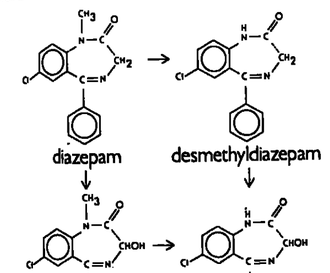
Injectable Valium has distinct anticonvulsant properties. Sample of EEG's in a patient with status epilepticus – before and 15 seconds after Valium 8 mg I.V. Lombroso CT: *Neurology* 16:629-634, July 1966.



Preliminary studies in both animals and humans have suggested that Valium may also work at the spinal level by enhancing presynaptic inhibition, a mechanism believed to diminish spasm in skeletal muscle.

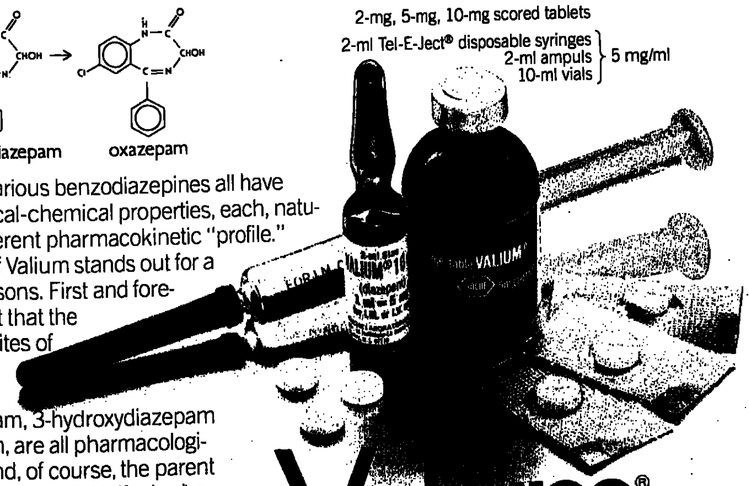
ROCHE

Only Valium (diazepam) has a pharmacokinetic profile that includes diazepam, active itself, plus other active metabolites



The unique metabolic pathways of Valium (diazepam)

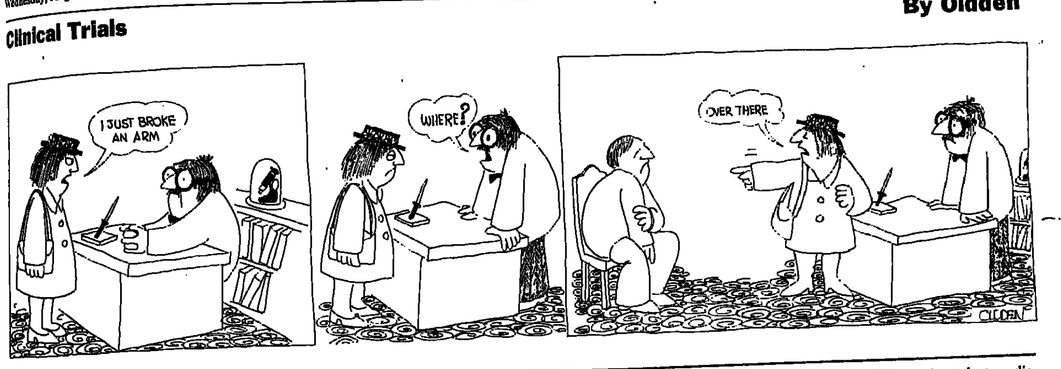
Because the various benzodiazepines all have different physical-chemical properties, each, naturally, has a different pharmacokinetic "profile." The "profile" of Valium stands out for a number of reasons. First and foremost is the fact that the major metabolites of Valium, which include desmethyldiazepam, 3-hydroxydiazepam and oxazepam, are all pharmacologically active. And, of course, the parent substance – diazepam itself – is also highly active. Then, too, Valium has demonstrated a highly reliable and consistent pattern of absorption, distribution, metabolism and excretion. Such pharmacokinetic predictability is just one more indication of its overall reliability of performance.



Valium® IV (diazepam)
One of a kind.

Please turn page for a summary of product information.

Clinical Trials **By Oldden**



TRIBUNE SPORTS REPORT

Steam Bath After Exercise Ups Cardiogenic Shock Risk

Medical Tribune Report

FORT COLLINS, COLO.—Steam baths combined with strenuous exercise may cause cardiogenic shock, particularly in middle-aged persons, and physicians should issue appropriate warnings to their patients, two sports medicine experts advise.

The level of risk depends on physical condition as well as how long and vigorously they exercise prior to or after the steam bath and the duration of exposure to the steam, Dr. Robert H. Pike, a former U.S. Olympic Team physician, told MEDICAL TRIBUNE. He called the dehydrating, oxygen-depriving atmosphere of steam baths a "non-physiological situation."

At Colorado State University here recently, two middle-aged men suffered myocardial infarctions after combining strenuous exercise and steam baths without a rest interval, Elliot Plese, Ph.D., Associate Professor of Physical Education, reported. One man had a history of cardiac disease and had complained of chest pains the previous night, Dr. Plese, who works with Dr. Pike, said in an interview. The victim had a "sweat box" session at the gym just before starting a handball game. "Instead of cooling off first," Dr. Plese explained, "the fellow went right into more strenuous activity, became even hotter, and suffered cardiogenic shock." Had this person played handball before going into the sweat box, the result would have been just as disastrous, he emphasized.

Steam baths as well as rubber gym garments are frequently resorted to by college wrestlers to make weight, Dr. Plese added. "But the body has no way of cooling itself with rubber garments," he said, adding that "using the steam bath does not assist youngsters in maintaining weight loss over a period of time."

Both men urge posting of warnings on steam bath doors.

All MDs Invited to Participate In International Cycle Race

Physicians of both sexes and all nationalities are invited to participate in international cycling race, like above, to be at Grammont, Belgium, Sept. 10-12, sponsored by *La Tribune Médical*, the French edition of MEDICAL TRIBUNE. Over 300 are registered already in race which will go 49 to 70 kilometers depending on entrant's age. Register before August 15, 1976, by writing to: Association Cyclistes Des Corps Sante, 10 Place Peyron, Marines, France.

IMMATERIA MEDICA

Synergetic Bucky Fuller

If you have 25 bucks, you can have a real vacation by taking a look at the way one of the most innovative minds of our time flies. We refer to R. Buckminister Fuller's $25 book, *Synergetics: Explorations in the Geometry of Thinking*, which Macmillan published and which is no one-night stand.

Largely self-taught, eccentric in his approach, and devastating to the conventional, he is the inventor of the Geodesic Dome, that marvel of stress lines which somehow becomes a sensible, highly useful home, the Dymaxion house, the Dymaxion car (which Detroit ought to reconsider because of its energy concepts), and much more. He has confounded mathematicians, industrialists, engineers and educators.

He has been so busy that so far as we know he never got around to straightening out medicine. He works on a larger scale. As he puts it, "We are going to have to find effective ways for all of humanity to see total Earth."

While a good many intelligent scientists faint dead away at his faith in technology, most of them are fascinated by his viewpoint of nature. He describes our vast industrial complex as "only of kindergarten magnitude compared to the complexity of the biological success of our planet Earth. In its complexities of design integrity, the Universe is technology . . . Man does not spontaneously recognize technology other than his own, so he speaks of the rest as something he ignorantly calls nature."

Or, as they call it in our cell-block, DNA!

While many have characterized "Bucky" as a genius, it's an appellation he declines. "I am not a genius, but I am a terrific package of experience," he says, but no one who has experienced his lectures or his books believes that. He *is* a genius.

So much so that in 1973 Hugh Kenner wrote a book titled *Bucky, A Guided Tour of Buckminister Fuller* (Morrow). A delightful introduction to this refreshing man, it is an almost necessary bit of equipment for coping with *Synergistics*.

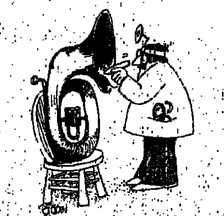
As Fuller describes it, "Synergy means behavior of whole systems unpredicted by the behavior of their parts taken separately." Although he calls it energetic geometry and experientially founded mathematics, some say this description could be applied to medicine.

A Columbia mathematics professor, after hearing Bucky lecture, said: "My only regret is that Euclid and Pythagoras could not have been here."

Bucky sums up the moral of his "experience"—he was 81 years old this past July 12—as: *"Dare to be naïve,"*

Have a good time.

Clinical Cliché



Patient had tubular breath sounds.